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(54) **TRICYCLIC INHIBITORS OF HEPATITIS B VIRUS**

(57) The present invention relates to compounds that are inhibitors of hepatitis B virus (HBV). Compounds of this invention are useful alone or in combination with other agents for treating, ameliorating, preventing or curing HBV infection and related conditions. The present invention also relates to pharmaceutical compositions containing said compounds.

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Description

FIELD OF THE INVENTION

[0001] The present invention relates to compounds that are inhibitors of hepatitis B virus (HBV). Compounds of this invention are useful alone or in combination with other agents for treating, ameliorating, preventing or curing HBV infection and related conditions. The present invention also relates to pharmaceutical compositions containing said compounds.

BACKGROUND OF THE INVENTION

[0002] The Hepatitis B virus (HBV) is an enveloped, partially double-stranded DNA (dsDNA) virus of the hepadnaviridae family that is spread by contact with infected blood and body fluids and causes acute and chronic necroinflammatory liver diseases of varying severity (Guidotti LG, Chisari FV. Annu Rev Pathol. 2006; 1:23-61). The HBV lipid envelope contains 3 in-frame viral envelope proteins (large, middle and small), each of which possesses the hepatitis B virus surface antigen (HBsAg) determinant (Seeger C, Mason WS.Virology. 2015 May; 479-480:672-86). This envelope encloses a protein shell, or capsid, that is composed of 240 monomers of the core protein and each monomer possesses the hepatitis B virus core antigen (HBcAg or Cp) determinant. The capsid in turn encloses a partially double-stranded, relaxed circular DNA (rcDNA) form of the viral genome as well as a molecule of the viral polymerase. Upon entry onto susceptible cells (i.e. the hepatocytes) via the interaction of the large envelope protein with specific receptors on the hepatocellular membrane, the capsid is released into the cytoplasm and transported at the nuclear membrane. The rcDNA is then released into the nucleus and repaired by cellular polymerases into an episomal "minichromosome", termed covalently closed circular DNA (cccDNA), which represents the viral transcriptional template. The minus strand of the viral DNA encodes 3.5, 2.4, 2.1 and 0.7 kb mRNA species that are translated into structural (envelope and core) and nonstructural (polymerase, precure and X) proteins of the virus. Following transport into the cytoplasm, one of the 3.5 kb RNAs (termed pregenomic RNA) is selectively packaged into a nascent capsid by interacting with the core and polymerase proteins that have been translated from their respective mRNAs. Within these capsids, the viral polymerase reverse transcribes the pregenomic RNA into a single minus strand DNA molecule that serves as template for the viral polymerase-mediated DNA plus strand synthesis and the cohesive structure of the linear DNA intermediates converts them into a relaxed circular double stranded molecule. A fraction of these HBV DNA-containing "mature" capsids are transported back to the nucleus where second strand synthesis is completed and the ends of both strands are ligated, leading to amplification of the pool of cccDNA. Another fraction of the capsids binds to viral envelope proteins that have been independently translated and translocated to membranes of endoplasmic reticulum (ER)-like structures. Following binding, the enveloped capsids bud into the lumen of the ER and exit the cell as infectious virions to initiate new cycles of infection.

[0003] Thus, the HBV core protein and the related capsids are essential components and regulators of the HBV life cycle. The full-length core protein Cp183, or its N-terminal domain Cp149, predominantly assembles into a T = 4 icosahedral capsids. Due to its critical roles in capsid assembly, pregenomic RNA packaging, and cccDNA maintenance, it is not surprising that the HBV core protein and the related capsids have been widely recognized as attractive antiviral targets (Durantel D, Zoulim F; J Hepatol. 2016 Apr;64(1 Suppl):S117-S131).

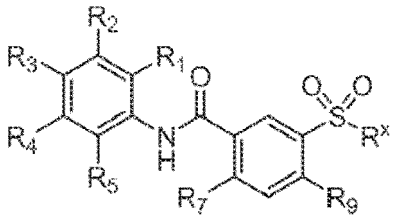
[0004] According to World Health Organization (WHO) statistics, HBV infection is one of the major medical scourges of our time. As a sexually transmitted disease that is also transferred by intravenous drug abuse and from mother to infant at birth, over one third of the world's population has been infected by HBV at some point in their lives (Burns GS, Thompson AJ; Cold Spring Harb Perspect Med. 2014 Oct 30;4(12)). While most of these people have successfully cleared the virus, more than 240 million people remain persistently infected and almost 800,000 of these individuals die annually from the complications of chronic infection (i.e. cirrhosis and/or hepatocellular carcinoma). HBV infection is highly endemic in sub-Saharan Africa, the Pacific, and particularly Asia. Regions with high rates of chronic HBV infection also include the Middle East, the Indian subcontinent, areas of South and Central America, and the southern parts of Eastern and Central Europe. In recent years the number of chronic carriers has increased steadily in the western world as well, mostly because of the influx of immigrants from endemic areas. Additionally, HBV acts as a helper virus to hepatitis delta virus (HDV) and it should be noted that the more than 15 million people co-infected with HBV and HDV have an increased risk of rapid progression to cirrhosis and hepatic decompensation (Hughes, S.A. et al. Lancet 2011, 378, 73-85).

[0005] Well-tolerated vaccines that elicit neutralizing antibodies to HBsAg efficiently prevent de novo HBV infection, but have no therapeutic potential for the millions of people that are already persistently infected (Zoulim, Durantel D; Cold Spring Harb Perspect Med. 2015 Apr 1;5(4)). Therapy for these individuals mainly relies on direct acting antiviral (DAA) drugs (e.g. tenofovir, lamivudine, adefovir, entecavir or telbivudine) that suppress virus production but do not eradicate HBV from the liver, requiring lifelong treatment. Cohorts of patients still receive a therapy based on pegylated interferon-α (PEG-IFN-α), which has the advantages of limited treatment duration and higher rates of HBsAg serocon-

version but the relevant disadvantage of greater adverse effects. As such, the number of patients receiving PEG-IFN-α is progressively decreasing.

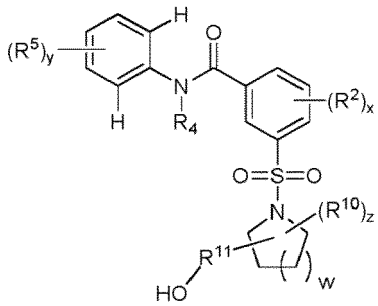
[0006] Different chemical classes of inhibitors targeting the encapsidation process of HBV (also termed capsid assembly modulators or CAMs) are under development, and they include heteroaryldihydropyrimidines (HAPs) and sulfamoylbenzamides (SBAs). For instance, Novira Therapeutics recently utilized a humanized mouse model of HBV infection to show that a combination of CAM and PEG-IFN-α has higher antiviral activity than that previously observed with DAAs. NVR3-778, the first member of this class of CAM, in Phase 1b proof-of-concept clinical studies showed both significant reduction in HBV DNA and serum HBV RNA. This compound was recently discontinued. The compound JNJ-56136379 (or JNJ-379), developed by Janssen, has recently demonstrated potent antiviral activity and is now entering into Phase 2 clinical trial.

[0007] WO2013/006394, published on January 10, 2013, relates to a subclass of sulfamoyl-arylamides having general formula A, useful for the treatment of Hepatitis B virus (HBV) infection:



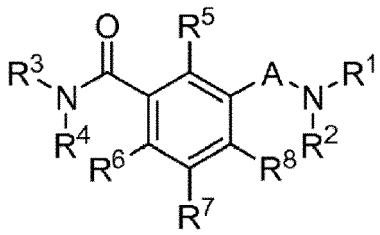
(A)

[0008] WO2013/096744, published on June 26, 2013 relates to sulfamoyl-arylamides of formula B active against HBV:



(B)

[0009] WO2014/106019, published on July 3, 2014, relates to compounds of formula C, useful as nucleocapsid assembly inhibitors for the treatment of viruses, especially but not exclusively, including pregenomic RNA encapsidation inhibitors of HBV for the treatment of Hepatitis B virus (HBV) infection and related conditions:



(C)

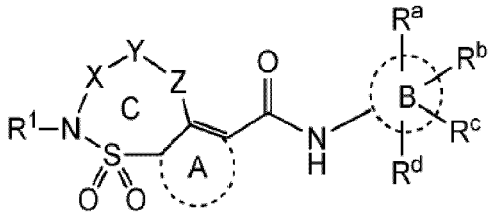
[0010] WO2014/165128, published on October 9, 2014, WO2015/109130 published on July 23, 2015, US2015274652, published on October 1, 2015, all relate to sulfamoyl-arylamides compounds active against HBV.

[0011] WO2015/120178, published on August 13, 2015, relates to sulfamoyl-arylamides compounds used in combinantion therapy with peginterferon alfa-2a, or another interferon analog for the treatment of HBV infection.

[0012] WO2016/089990, published on June 9, 2016, relates to sulfide alkyl and pyridyl reverse sulphonamide compounds for HBV treatment.

[0013] US2016185748, published on June 30, 2016, relates to pyridyl reverse sulfonamides for HBV treatment.

[0014] US2016151375, published on June 2, 2016 relates to sulfide alkyl compounds for HBV treatment. WO2017/001655A1, published on January 5, 2017, relates to cyclized sulfamoylarylamide derivatives having structure:



(D)

[0015] Amongst the problems which HBV direct antivirals may encounter are toxicity, mutagenicity, lack of selectivity, poor efficacy, poor bioavailability, low solubility and/or off-target activity, and until now there are no compounds in any of the structural classes identified above approved as drugs for the treatment of HBV patients.

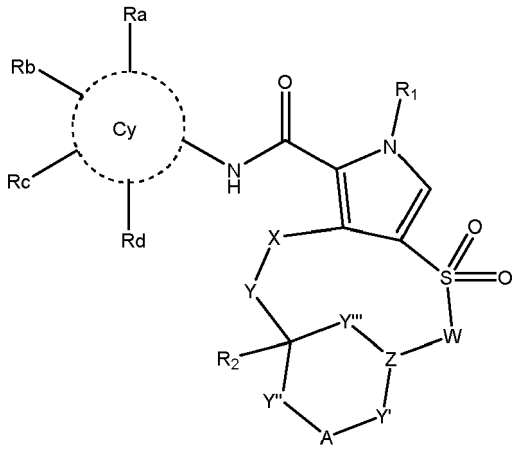
[0016] There is a need for additional HBV inhibitors that may overcome at least one of these disadvantages or that have additional advantages such as increased potency, increased bioavailability or an increased safety window.

[0017] The present invention provides small molecule drugs obtained through chemical modification of the known sulfamoyl arylamides derivatives. In particular the compound of the invention are characterized by a fused tricyclic core structure comprising a pyrrole ring. The chemotype discovered in the present invention results in potent HBV inhibitors with improved pharmacokinetic properties, good kinetic solubility, stability in mouse and human hepatocytes, low in vivo clearance and positive liver-to-plasma concentration. Given the liver's key role in metabolic regulation and the fact that it is the principal tissue affected by hepatitis B disease, designing HBV inhibitors with hepatoselective distribution profiles is an important strategy in developing safe drug candidates (Tu M. et al., Current Topics in Medicinal Chemistry, 2013, 13, 857-866).

DESCRIPTION OF THE INVENTION

[0018] The compounds of this invention are inhibitors of hepatitis B virus (HBV).

[0019] It is therefore an object of the present invention a compound of general formula (I):



(I)

wherein:

Cy is aryl or heteroaryl;
X is O, NH or N-C_{1-6}alkyl;
Y, Y', Y'' and Y''' are each independently a single bond or C_{1-6}alkanediyl optionally substituted with one or more R_3;
Z is CR_4 or N;

W is a single bond or NR_5, wherein if W is a single bond, Z is N, and if W is NR_5, Z is CR_4;
A is NR_6, O, S or C_{1-6}alkanediyl optionally substituted with one or more R_3;
R_1 is H or C_{1-6}alkyl;
R_2 is selected from H, OH and C_{1-6}alkyl;
R_3 is selected from H, OH, C_{1-6}alkyl, C_{3-8}cycloalkyl and halogen or two geminal R_3 form together with the atom to which they are attached a spiro-C_{3-8}cycloalkyl or a spiro-C_{3-8}heterocycloalkyl; R_4 is H or C_{1-6}alkyl;
or when W is NR_5 and Z is CR_4, R_2 and R_4 may optionally form a C_{1-6}alkanediyl bridge;
R_5 is selected from H, C_{1-6}alkyl, C_{1-6}alkylaryl, C_{1-6}alkylheteroaryl and C_{1-6}alkyl-C_{3-8}cycloalkyl wherein each of said C_{1-6}alkyl, C_{1-6}alkylaryl, C_{1-6}alkylheteroaryl or C_{1-6}alkyl-C_{3-8}cycloalkyl is optionally substituted with one or more substituents each independently selected from: OH, halogen, haloC_{1-6}alkyl, cyano and NH_2;
R_6 is selected from:

- hydrogen;
- OH;
- $C(O)R_7$;
- $C(O)OR_7$;
- $C(O)NHR_7$;
- $C(O)N(R_7)_2$;
- SO_2R_7;
- $SO_2NH(R_7)$;
- $SO_2N(R_7)_2$;
- C_{1-6}alkyl optionally substituted with one or more substituents each independently selected from the group consisting of: OH, halogen, CN, NH_2, $NH(R_7)$, $N(R_7)_2$, aryl, heteroaryl, 3-7 membered saturated ring and 5-7 membered unsaturated ring, each of said saturated or unsaturated ring optionally containing one or more heteroatoms selected from the group consisting of O, N and S and each of said aryl, heteroaryl, 3-7 membered saturated or 5-7 membered unsaturated ring being optionally substituted with one or more substituents each independently selected from OH, halogen, haloC_{1-6}alky 1, CN, haloC_{1-6}alkoxy and C_{1-6}alkoxy;
- aryl or heteroaryl ring, each of said aryl or heteroaryl ring being optionally substituted with one or more substituents each independently selected from: OH, halogen, haloC_{1-6}alkyl, CN, haloC_{1-6}alkoxy and C_{1-6}alkoxy; and
- a 3-8 membered saturated or partially unsaturated cyclic or bicyclic ring optionally containing one or more heteroatoms each independently selected from the group consisting of: O, S and N, the 3-8 membered saturated or partially unsaturated cyclic or bicyclic ring being optionally substituted with one, two or more substituents each independently selected from the group consisting of: OH, halogen, CN, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, $C(O)OR_7$, $C(O)R_7$, haloC_{1-6}alkyl, haloC_{1-6}alkoxy and C_{1-6}alkoxy;

R_7 is selected from the group consisting of: C_{1-6}alkyl, C_{3-8}cycloalkyl, aryl, heteroaryl and 3-8 membered saturated or partially saturated heterocyclic ring, wherein each of said C_{1-6}alkyl, C_{3-8}cycloalkyl, aryl, heteroaryl or 3-8 membered saturated or partially saturated heterocyclic ring is optionally substituted with one or more substituents each independently selected from the group consisting of: OH, halogen, CN, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, haloC_{1-6}alkyl, haloC_{1-6}alkoxy and C_{1-6}alkoxy;
Ra, Rb, Rc and Rd are each idependently selected from the group consisting of: hydrogen, halogen, CN, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl and haloC_{1-6}alkoxy;
and pharmaceutically acceptable salts, tautomers, isomers, stereoisomers thereof.

[0020] Preferably, Cy is aryl. Still preferably, Cy is phenyl.

[0021] Preferably, X is O or NH. Still preferably, X is O.

[0022] Preferably, Y, Y' and Y" are each idependently a single bond or an unsubstituted C_{1-4}alkanediyl. More preferably, Y, Y' and Y" are each idependently methanediyl. Preferably, Y'" is a single bond. Preferably, Y and Y" are the same and are both a single bond or an unsubstituted C_{1-4}alkanediyl. More preferably, Y and Y" are the same and are both methanediyl.

[0023] Preferably, Z is CH or N. Still preferably, Z is CH.

[0024] Preferably, W is a single bond or NH. More preferably, W is NH.

[0025] Preferably, A is NR_6 or unsubstituted C_{1-4}alkanediyl. More preferably, A is NR_6 or methanediyl. Also preferably, A is NR_6 or methanediyl and Y' and Y" are the same and are both methanediyl. Preferably, R_1 is C_{1-6}alkyl. More preferably, R_1 is methyl.

[0026] Preferably, R_2 is H, OH or methyl. More preferably, R_2 is H.

[0027] Preferably, R_3 is H. Preferably, R_4 is H. Preferably, R_5 is H.

[0028] Preferably, R_6 is selected from: hydrogen, $C(O)OR_7$, $C(O)NHR_7$, SO_2R_7, $SO_2NH(R_7)$ and unsubstitued C_1-

$_6$alkyl. Still preferably, R_6 is selected from: hydrogen, C(O)OEt, C(O)OtBu, C(O)NHMe, SO_2iPr, SO_2Me, SO_2cyclopropyl, SO_2NHiPr and methyl.

[0029] Preferably, R_7 is C_{1-6}alkyl or a 3-8 membered saturated heterocyclic ring. More preferably, R_7 selected from: ethyl, *i*-propyl, methyl, cyclopropyl, *t*-butyl and hexahydrofuro[2,3-b]furan system. Preferably, Ra, Rb, Rc and Rd are each idependently selected from the group consisting of: hydrogen, halogen, CN, C_{1-6}alkyl and haloC_{1-6}alkyl. More preferably, Ra, Rb, Rc and Rd are each idependently selected from the group consisting of: hydrogen, fluorine, chlorine, methyl, CN and CHF_2.

[0030] Preferably at least one of Ra, Rb, Rc and Rd is halogen, more preferably fluorine, and the other(s) is/are hydrogen.

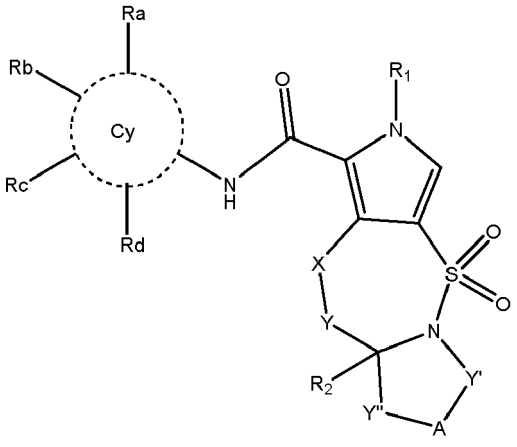
[0031] Preferably, at least two of Ra, Rb, Rc and Rd are each idependently selected from the group consisting of: hydrogen, halogen, CN, C_{1-6}alkyl and haloC_{1-6}alkyl. More preferably, at least two of Ra, Rb, Rc and Rd are each idependently selected from the group consisting of: hydrogen, fluorine, chlorine, methyl, CN and CHF_2.

[0032] Preferably, at least three of Ra, Rb, Rc and Rd are each idependently selected from the group consisting of: hydrogen, halogen, CN, C_{1-6}alkyl and haloC_{1-6}alkyl. More preferably, at least three of Ra, Rb, Rc and Rd are each idependently selected from the group consisting of: hydrogen, fluorine, chlorine, methyl, CN and CHF_2.

[0033] Preferably, two of Ra, Rb, Rc and Rd are halogen, more preferably fluorine.

[0034] Preferably, three of Ra, Rb, Rc and Rd are halogen, more preferably fluorine.

[0035] It is a further object of the invention a compound having general formula (Ia):



(Ia)

wherein:

Cy is aryl or heteroaryl;
X is O, NH or N-C_{1-6}alkyl;
Y, Y' and Y" are each independently a single bond or C_{1-6}alkanediyl optionally substituted with one or more R_3;
A is NR_6, O, S or C_{1-6}alkanediyl optionally substituted with one or more R_3;
R_1 is H or C_{1-6}alkyl;
R_2 is selected from H, OH and C_{1-6}alkyl;
R_3 is selected from H, OH, C_{1-6}alkyl, C_{3-8}cycloalkyl and halogen or two geminal R_3 form together with the atom to which they are attached a spiro-C_{3-8}cycloalkyl or a spiro-C_{3-8}heterocycloalkyl; R_6 is selected from:

- hydrogen;
- OH;
- $C(O)R_7$;
- $C(O)OR_7$;
- $C(O)NHR_7$;
- $C(O)N(R_7)_2$;
- SO_2R_7;
- $SO_2NH(R_7)$;
- $SO_2N(R_7)_2$;
- C_{1-6}alkyl optionally substituted with one or more substituents each independently selected from the group consisting of: OH, halogen, CN, NH_2, $NH(R_7)$, $N(R_7)_2$, aryl, heteroaryl, 3-7 membered saturated ring and 5-7 membered unsaturated ring, each of said saturated or unsaturated ring optionally containing one or more

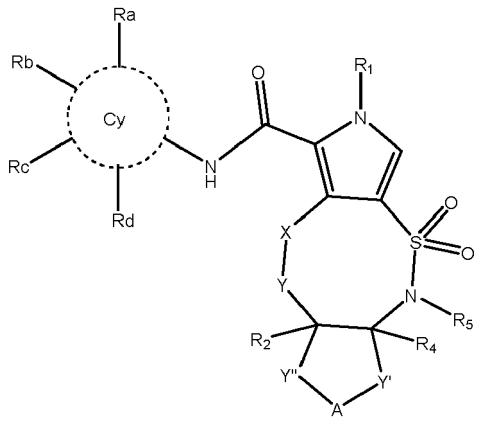
heteroatoms selected from the group consisting of O, N and S and each of said aryl, heteroaryl, 3-7 membered saturated or 5-7 membered unsaturated ring being optionally substituted with one or more substituents each independently selected from OH, halogen, haloC_{1-6}alky 1, CN, haloC_{1-6}alkoxy and C_{1-6}alkoxy;

- aryl or heteroaryl ring, each of said aryl or heteroaryl ring being optionally substituted with one or more substituents each independently selected from: OH, halogen, haloC_{1-6}alkyl, CN, haloC_{1-6}alkoxy and C_{1-6}alkoxy; and
- a 3-8 membered saturated or partially unsaturated cyclic or bicyclic ring optionally containing one or more heteroatoms each independently selected from the group consisting of: O, S and N, the 3-8 membered saturated or partially unsaturated cyclic or bicyclic ring being optionally substituted with one, two or more substituents each independently selected from the group consisting of: OH, halogen, CN, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, $C(O)OR_7$, $C(O)R_7$, haloC_{1-6}alkyl, haloC_{1-6}alkoxy and C_{1-6}alkoxy;

R_7 is selected from the group consisting of: C_{1-6}alkyl, C_{3-8}cycloalkyl, aryl, heteroaryl and 3-8 membered saturated or partially saturated heterocyclic ring, wherein each of said C_{1-6}alkyl, C_{3-}scycloalkyl, aryl, heteroaryl or 3-8 membered saturated or partially saturated heterocyclic ring is optionally substituted with one or more substituents each independently selected from the group consisting of: OH, halogen, CN, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, haloC_{1-6}alkyl, haloC_{1-6}alkoxy and C_{1-6}alkoxy;
Ra, Rb, Rc and Rd are each idependently selected from the group consisting of: hydrogen, halogen, CN, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl and haloC_{1-6}alkoxy;
and pharmaceutically acceptable salts, tautomers, isomers, stereoisomers thereof.

[0036] In a preferred embodiment, the invention provides a compound having general formula (Ia) as defined above, wherein Cy is phenyl, and/or X is O or NH, and/or A is CH_2, and/or R_1 is CH_3, and/or R_2 is hydrogen and/or R_3 is hydrogen and pharmaceutically acceptable salts, tautomers, isomers, stereoisomers thereof. Preferably, Cy is phenyl, X is O or NH, A is CH_2, R_1 is CH_3, R_2 and R_3 are hydrogen.

[0037] It is a further object of the invention a compound having general formula (Ib):



(Ib)

wherein:

Cy is aryl or heteroaryl;
X is O, NH or N-C_{1-6}alkyl;
Y, Y' and Y" are each independently a single bond or C_{1-6}alkanediyl optionally substituted with one or more R_3;
A is NR_6, O, S or C_{1-6}alkanediyl optionally substituted with one or more R_3;
R_1 is H or C_{1-6}alkyl;
R_2 is selected from H, OH and C_{1-6}alkyl;
R_3 is selected from H, OH, C_{1-6}alkyl, C_{3-8}cycloalkyl and halogen or two geminal R_3 form together with the atom to which they are attached a spiro-C_{3-8}cycloalkyl or a spiro-C_{3-8}heterocycloalkyl;
R_4 is H or C_{1-6}alkyl;
or R_2 and R_4 may optionally form a C_{1-6}alkanediyl bridge;
R_5 is selected from H, C_{1-6}alkyl, C_{1-6}alkylaryl, C_{1-6}alkylheteroaryl and C_{1-6}alkyl-C_{3-8}cycloalkyl wherein each of said C_{1-6}alkyl, C_{1-6}alkylaryl, C_{1-6}alkylheteroaryl or C_{1-6}alkyl-C_{3-8}cycloalkyl is optionally substituted with one or more substituents each independently selected from: OH, halogen, haloC_{1-6}alkyl, cyano and NH_2;
R_6 is selected from:

- hydrogen;
- OH;
- $C(O)R_7$;
- $C(O)OR_7$;
- $C(O)NHR_7$;
- $C(O)N(R_7)_2$;
- SO_2R_7;
- $SO_2NH(R_7)$;
- $SO_2N(R_7)_2$;
- C_{1-6}alkyl optionally substituted with one or more substituents each independently selected from the group consisting of: OH, halogen, CN, NH_2, $NH(R_7)$, $N(R_7)_2$, aryl, heteroaryl, 3-7 membered saturated ring and 5-7 membered unsaturated ring, each of said saturated or unsaturated ring optionally containing one or more heteroatoms selected from the group consisting of O, N and S and each of said aryl, heteroaryl, 3-7 membered saturated or 5-7 membered unsaturated ring being optionally substituted with one or more substituents each independently selected from OH, halogen, haloC_{1-6}alky 1, CN, haloC_{1-6}alkoxy and C_{1-6}alkoxy;
- aryl or heteroaryl ring, each of said aryl or heteroaryl ring being optionally substituted with one or more substituents each independently selected from: OH, halogen, halo C_{1-6}alkyl, CN, haloC_{1-6}alkoxy and C_{1-6}alkoxy; and
- a 3-8 membered saturated or partially unsaturated cyclic or bicyclic ring optionally containing one or more heteroatoms each independently selected from the group consisting of: O, S and N, the 3-8 membered saturated or partially unsaturated cyclic or bicyclic ring being optionally substituted with one, two or more substituents each independently selected from the group consisting of: OH, halogen, CN, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, $C(O)OR_7$, $C(O)R_7$, haloC_{1-6}alkyl, haloC_{1-6}alkoxy and C_{1-6}alkoxy;

R_7 is selected from the group consisting of: C_{1-6}alkyl, C_{3-8}cycloalkyl, aryl, heteroaryl and 3-8 membered saturated or partially saturated heterocyclic ring, wherein each of said C_{1-6}alkyl, C_{3-8}cycloalkyl, aryl, heteroaryl or 3-8 membered saturated or partially saturated heterocyclic ring is optionally substituted with one or more substituents each independently selected from the group consisting of: OH, halogen, CN, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, haloC_{1-6}alkyl, haloC_{1-6}alkoxy and C_{1-6}alkoxy;
Ra, Rb, Rc and Rd are each idependently selected from the group consisting of: hydrogen, halogen, CN, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl and haloC_{1-6}alkoxy;
and pharmaceutically acceptable salts, tautomers, isomers, stereoisomers thereof.

[0038] In a preferred embodiment, the invention provides a compound having general formula (Ib) as defined above, wherein Cy is phenyl, and/or X is O, and/or Y is CH_2, and/or Y' is CH_2, and/or Y" is CH_2, and/or A is CH_2, O or NR_6 and pharmaceutically acceptable salts, tautomers, isomers, stereoisomers thereof. Preferably, Cy is phenyl, X is O, Y is CH_2, Y' is CH_2, Y" is CH_2, and A is CH_2, O or NR_6.

[0039] Preferably, Cy is phenyl; and/or X is O; and/or Y is a single bond or methanediyl; and/or R_1 is methyl; and/or R_2 is H.

[0040] In a preferred embodiment compounds of the invention are selected from the following list:

- N-(3,4-difluorophenyl)-2-methyl-6,7,8,9,9a,10-hexahydro-2H-pyrido[1,2-e]pyrrolo[3,4-b][1,4,5]oxathiazepine-1-carboxamide 4,4-dioxide;
- N-(3,4-difluorophenyl)-2-methyl-2,6,7,8,9,9a,10,11-octahydropyrido[1,2-b]pyrrolo[3,4-f][1,2,5]thiadiazepine-1-carboxamide 4,4-dioxide;
- N-(3,4-difluorophenyl)-2-methyl-6,7,7a,8-tetrahydro-2H-azeto[1,2-e]pyrrolo[3,4-b][1,4,5]oxathiazepine-1-carboxamide 4,4-dioxide;
- *trans*-N-(3,4-difluorophenyl)-7-methyl-1,3a,4,9a-tetrahydro-3H,7H-furo[3,4-f]pyrrolo[3,4-b][l,4,5]oxathiazepine-8-carboxamide 5,5-dioxide;
- *cis*-N-(3,4-difluorophenyl)-9-methyl-3,4,5,6-tetrahydro-2H,9H-3,5-methanopyrrolo[3,4-b][1,4,5]oxathiazonine-8-carboxamide 1,1-dioxide;
- *cis*-N-(3,4-difluorophenyl)-2-methyl-5a,6,7,8,8a,9-hexahydro-2H,5H-cyclopenta[f]pyrrolo[3,4-b][1,4,5]oxathiazocine-1-carboxamide 4,4-dioxide;
- *trans*-7-methyl-N-(3,4,5-trifluorophenyl)-1,3a,4,9a-tetrahydro-3H,7H-furo[3,4-f]pyrrolo[3,4-b][1,4,5]oxathiazepine-8-carboxamide 5,5-dioxide;
- (5aR,8aR)-N-(3,4-difluorophenyl)-2-methyl-5a,6,7,8,8a,9-hexahydro-2H,5H-cyclopenta[f]pyrrolo[3,4-b][1,4,5]oxathiazocine-1-carboxamide 4,4-dioxide;
- (5aS,8aS)-N-(3,4-difluorophenyl)-2-methyl-5a,6,7,8,8a,9-hexahydro-2H,5H-cyclopenta[f]pyrrolo[3,4-b][1,4,5]oxathiazocine-1-carboxamide 4,4-dioxide;

- *cis*-Ethyl 7-methyl-8-((3,4,5-trifluorophenyl)carbamoyl)-3a,4,10,10a-tetrahydro-1H,7H-dipyrrolo[3,4-b:3',4'-f][1,4,5]oxathiazocine-2(3H)-carboxylate 5,5-dioxide;
- *cis*- 7-methyl-N-(3,4,5-trifluorophenyl)-2,3,3a,4,10,10a-hexahydro-1H,7H-dipyrrolo[3,4-b:3',4'-f][l,4,5]oxathiazocine-8-carboxamide 5,5-dioxide;
- *cis*-2,7-dimethyl-N-(3,4,5-trifluorophenyl)-2,3,3a,4,10,10a-hexahydro-1H,7H-dipyrrolo[3,4-b:3',4'-f][1,4,5]oxathiazocine-8-carboxamide 5,5-dioxide;
- *cis*-Ethyl 8-((3,4-difluorophenyl)carbamoyl)-7-methyl-3a,4,10,10a-tetrahydro-1H,7H-dipyrrolo[3,4-b:3',4'-f][1,4,5]oxathiazocine-2(3H)-carboxylate 5,5-dioxide;
- *cis*-Ethyl 8-((4-fluoro-3-methylphenyl)carbamoyl)-7-methyl-3a,4,10,10a-tetrahydro-1H,7H-dipyrrolo[3,4-b:3',4'-f][1,4,5]oxathiazocine-2(3H)-carboxylate 5,5-dioxide;
- *cis*-Ethyl 8-((3-chloro-4-fluorophenyl)carbamoyl)-7-methyl-3a,4,10, 10a-tetrahydro-1H,7H-dipyrrolo[3,4-b:3',4'-f][1,4,5]oxathiazocine-2(3H)-carboxylate 5,5-dioxide;
- *cis*-Ethyl 8-((3-(difluoromethyl)-4-fluorophenyl)carbamoyl)-7-methyl-3a,4,10,10a-tetrahydro-1H,7H-dipyrrolo[3,4-b:3',4'-f][1,4,5]oxathiazocme-2(3H)-carboxylate 5,5-dioxide;
- *cis*-Ethyl 8-((3-cyano-4-fluorophenyl)carbamoyl)-7-methyl-3a,4,10,10a-tetrahydro-1H,7H-dipyrrolo[3,4-b:3',4'-f][1,4,5]oxathiazocine-2(3H)-carboxylate 5,5-dioxide;
- *cis*-2-(isopropylsulfonyl)-7-methyl-N-(3,4,5-trifluorophenyl)-2,3,3a,4,10,10a-hexahydro-1H,7H-dipyrrolo[3,4-b:3',4'-f][1,4,5]oxathiazocine-8-carboxamide 5,5-dioxide;
- *cis*-7-methyl-2-(methylsulfonyl)-N-(3,4,5-trifluorophenyl)-2,3,3a,4,10,10a-hexahydro-1H,7H-dipyrrolo[3,4-b:3',4'-f][1,4,5]oxathiazocme-8-carboxamide 5,5-dioxide;
- *cis*-2-(cyclopropylsulfonyl)-7-methyl-N-(3,4,5-trifluorophenyl)-2,3,3a,4,10,10a-hexahydro-1H,7H-dipyrrolo[3,4-b:3',4'-f][1,4,5]oxathiazocme-8-carboxamide 5,5-dioxide;
- *cis*-2-(N-isopropylsulfamoyl)-7-methyl-N-(3,4,5-trifluorophenyl)-2,3,3a,4,10,10a-hexahydro-1H,7H-dipyrrolo[3,4-b:3',4'-f][1,4,5]oxathiazocme-8-carboxamide 5,5-dioxide;
- cis-(3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-yl 7-methyl-8-((3,4,5-trifluorophenyl)carbamoyl)-3a,4,10,10a-tetrahydro-1H,7H-dipyrrolo[3,4-b:3',4'-f][1,4,5]oxathiazocine-2(3H)-carboxylate 5,5-dioxide;
- N^2,7-dimethyl-N^8-(3,4,5-trifluorophenyl)-3a,4,10,10a-tetrahydro-1H,7H-dipyrrolo[3,4-b:3',4'-f][1,4,5]oxathiazocine-2,8(3H)-dicarboxamide 5,5-dioxide;
- tert-butyl 7-methyl-8-((3,4,5-trifluorophenyl)carbamoyl)-3a,4,10,10a-tetrahydro-1H,7H-dipyrrolo[3,4-b:3',4'-f][1,4,5]oxathiazocine-2(3H)-carboxylate 5,5-dioxide;
- (3aR,10aS)-N-(3,4-difluorophenyl)-7-methyl-2,3,3a,4,10,10a-hexahydro-1H,7H-dipyrrolo[3,4-b:3',2'-f][1,4,5]oxathiazocme-8-carboxamide 5,5-dioxide;
- (3aR,10aS)-N8-(3,4-difluorophenyl)-N1,7-dimethyl-2,3,3a,4,10,10a-hexahydro-1H,7H-dipyrrolo[3,4-b:3',2'-f][1,4,5]oxathiazocme-1,8-dicarboxamide 5,5-dioxide;
- ethyl (3aR,10aS)-8-((3,4-difluorophenyl)carbamoyl)-7-methyl-2,3,3a,4,10,10a-hexahydro-1H,7H-dipyrrolo[3,4-b:3',2'-f][1,4,5]oxathiazocine-1-carboxylate 5,5-dioxide;
- *cis*-2-methyl-N-(3,4,5-trifluorophenyl)-5a,6,7,8,8a,9-hexahydro-2H,5H-cyclopenta[f]pyrrolo[3,4-b][1,4,5]oxathiazocine-1-carboxamide 4,4-dioxide;
- N-(3,4-difluorophenyl)-2,8a-dimethyl-5a,6,7,8,8a,9-hexahydro-2H,5H-cyclopenta[f]pyrrolo[3,4-b][1,4,5]oxathiazocine-1-carboxamide 4,4-dioxide;
- *cis*-N-(3,4-difluorophenyl)-8a-hydroxy-2-methyl-5a,6,7,8,8a,9-hexahydro-2H,5H-cyclopenta[f]pyrrolo[3,4-b][1,4,5]oxathiazocine-1-carboxamide 4,4-dioxide;
- (3aS,10aS)-7-methyl-N-(3,4,5-trifluorophenyl)-2,3,3a,4,10,10a-hexahydro-1H,7H-dipyrrolo[3,4-b:3',4'-f][1,4,5]oxathiazocine-8-carboxamide 5,5-dioxide;
- (3aR,10aR)-7-methyl-N-(3,4,5-trifluorophenyl)-2,3,3a,4,10,10a-hexahydro-1H,7H-dipyrrolo[3,4-b:3',4'-f][1,4,5]oxathiazocine-8-carboxamide 5,5-dioxide;
- ethyl (3aR,10aR)-7-methyl-8-((3,4,5-trifluorophenyl)carbamoyl)-3a,4,10,10a-tetrahydro-1H,7H-dipyrrolo[3,4-b:3',4'-f][1,4,5]oxathiazocine-2(3H)-carboxylate 5,5-dioxide;
- ethyl (3aS,10aS)-7-methyl-8-((3,4,5-trifluorophenyl)carbamoyl)-3a,4,10,10a-tetrahydro-1H,7H-dipyrrolo[3,4-b:3',4'-f][1,4,5]oxathiazocine-2(3H)-carboxylate 5,5-dioxide;
- tert-butyl (3aS,10aS)-7-methyl-8-((3,4,5-trifluorophenyl)carbamoyl)-3a,4,10,10a-tetrahydro-1H,7H-dipyrrolo[3,4-b:3',4'-f][1,4,5]oxathiazocine-2(3H)-carboxylate 5,5-dioxide;
- tert-butyl (3aR,10aR)-7-methyl-8-((3,4,5-trifluorophenyl)carbamoyl)-3a,4,10,10a-tetrahydro-1H,7H-dipyrrolo[3,4-b:3',4'-f][1,4,5]oxathiazocine-2(3H)-carboxylate 5,5-dioxide;
- (5aS,8aR) N-(3,4-difluorophenyl)-2-methyl-5a,6,7,8,8a,9-hexahydro-2H,5H-cyclopenta[f]pyrrolo[3,4-b][1,4,5]oxathiazocine-1-carboxamide 4,4-dioxide;
- (5aR,8aS) N-(3,4-difluorophenyl)-2-methyl-5a,6,7,8,8a,9-hexahydro-2H,5H-cyclopenta[f]pyrrolo[3,4-b][1,4,5]oxathiazocine-1-carboxamide 4,4-dioxide;

and pharmaceutically acceptable salts, tautomers, isomers, stereoisomers thereof.

[0041] Preferred compounds exhibit an HBV inhibition and/or an EC_{50}, as defined hereinbelow, greater than 50%.

[0042] Preferably, the compounds as defined above are for medical use. Still preferably, the compounds as defined above are for use in the treatment and/or prevention of a HBV infection.

[0043] Even more preferably, the compounds of the invention are used in treating, eradicating, reducing, slowing or inhibiting an HBV infection in an individual in need thereof, and/or in reducing the viral load associated with an HBV infection in an individual in need thereof, and/or reducing reoccurrence of an HBV infection in an individual in need thereof, and/or inducing remission of hepatic injury from an HBV infection in an individual in need thereof, and/or prophylactically treating an HBV infection in an individual afflicted with a latent HBV infection.

[0044] Preferably, the compound as defined above is for use in combination with at least one further therapeutic agent. Preferably, said use in combination comprises the administration of at least one therapeutic agent.

[0045] It is an object of the invention a pharmaceutical composition comprising the compound as defined above, alone or in combination with at least one further therapeutic agent, and at least one pharmaceutically acceptable excipient.

[0046] Preferably, the at least one further therapeutic agent is selected from the group consisting of: a therapeutic vaccine; an RNA interference therapeutic/antisense oligonucleotide; an immunomodulator; a STING agonist; a RIG-I modulator; a NKT modulator; an IL agonist; an interleukin or another immune acting protein; a therapeutic and prophylactic vaccine; an immune checkpoint modulator/inhibitor; an HBV entry inhibitor; a cccDNA modulator; an inhibitor of HBV protein espression; an agent targeting HBV RNA; a capsid assembly inhibitor/modulator; a core or X protein targeting agent; a nucleotide analogue; a nucleoside analogue; an interferon or a modified interferon; an HBV antiviral of distinct or unknown mechanism; a cyclophilin inhibitor; a sAg release inhibitor; a HBV polymerase inhibitor; a dinucleotide; a SMAC inhibitor; a HDV targeting agent; a viral maturation inhibitor; a reverse transcriptase inhibitor and an HBV RNA destabilizer or another small-molecule inhibitor of HBV protein expression; or a combination thereof.

[0047] Preferably, the therapeutic vaccine is selected from: HBsAG-HBIG, HB-Vac, ABX203, NASVAC, GS-4774, GX-110 (HB-110E), CVI-HBV-002, RG7944 (INO-1800), TG-1050, FP-02 (Hepsyn-B), AIC649, VGX-6200, KW-2, TomegaVax-HBV, ISA-204, NU-500, INX-102-00557, HBV MVA and PepTcell.

[0048] Preferably, the RNA interference therapeutic is a siRNA, a ddRNA or a shRNA. Preferably, the RNA interference therapeutic is selected from: TKM-HBV (ARB-1467), ARB-1740, ARC-520, ARC-521, BB-HB-331, REP-2139, ALN-HBV, ALN-PDL, LUNAR-HBV, GS3228836 and GS3389404.

[0049] Preferably, the immunomodulator is a TLR agonist. Preferably the TLR agonist is a TLR7, TLR8 or TLR9 agonist. Preferably, the TLR7, TLR8 or TLR9 agonist is selected from: RG7795 (RO-6864018), GS-9620, SM360320 (9-benzyl-8-hydroxy-2-(2-methoxy-ethoxy)adenine), AZD 8848 (methyl [3-({[3-(6-amino-2-butoxy-8-oxo-7,8-dihydro-9H-pyrin-9-yl)propyl][3-(4-morpholinyl)propyl]amino}methyl)phenyl]acetate) and ARB-1598.

[0050] Preferably, the RIG-I modulator is SB-9200. Preferably, the IL agonist or other immune acting protein is INO-9112 or recombinant IL12. Preferably, the immune checkpoint modulator/inhibitor is BMS-936558 (Opdivo (nivolumab)) or pembrolizumab. Preferably, the HBV entry inhibitor is Myrcludex B, IVIG-Tonrol or GC-1102.

[0051] Preferably, the cccDNA modulator is selected from: a direct cccDNA inhibitor, an inhibitor of cccDNA formation or maintenance, a cccDNA epigenetic modifier and an inhibitor of cccDNA transcription.

[0052] Preferably, the capsid assembly inhibitor/modulator, core or X protein targeting agent, direct cccDNA inhibitor, inhibitor of cccDNA formation or maintenance, or cccDNA epigenetic modifier is selected from: BAY 41-4109, NVR 3-778, GLS-4, NZ-4 (W28F), Y101, ARB-423, ARB-199, ARB-596, AB-506, JNJ-56136379, ASMB-101 (AB-V102), ASMB-103, CHR-101, CC-31326, AT-130 and RO7049389.

[0053] Preferably, the interferon or modified interferon is selected from: interferon alpha (IFN-α), pegylated interferon alpha (PEG-IFN-α), interferon alpha-2a, recombinant interferon alpha-2a, peginterferon alpha-2a (Pegasys), interferon alpha-2b (Intron A), recombinant interferon alpha-2b, interferon alpha-2b XL, peginterferon alpha-2b, glycosylated interferon alpha-2b, interferon alpha-2c, recombinant interferon alpha-2c, interferon beta, interferon beta-la, peginterferon beta-la, interferon delta, interferon lambda (IFN-λ), peginterferon lambda-1, interferon omega, interferon tau, interferon gamma (IFN-γ), interferon alfacon-1, interferon alpha-nl, interferon alpha-n3, albinterferon alpha-2b, BLX-883, DA-3021, PI 101 (also known as AOP2014), PEG-infergen, Belerofon, INTEFEN-IFN, albumin/interferon alpha 2a fusion protein, rHSA-IFN alpha 2a, rHSA-IFN alpha 2b, PEG-IFN-SA and interferon alpha biobetter. Particularly preferred are: peginterferon alpha-2a, peginterferon alpha-2b, glycosylated interferon alpha-2b, peginterferon beta-la, and peginterferon lambda-1. More particularly preferred is peginterferon alpha-2a. Preferably, the HBV antiviral of distinct or unknown mechanism is selected from: AT-61 ((E)-N-(1-chloro-3-oxo-1-phenyl-3-(piperidin-1-yl)prop-1-en-2-yl)benzamide), AT130 ((E)-N-(1-bromo-1-(2-methoxyphenyl)-3-oxo-3-(piperidin-1-yl)prop-1-en-2-yl)-4-nitrobenzamide), analogues thereof, REP-9AC (REP-2055), REP-9AC' (REP-2139), REP-2165 and HBV-0259. Preferably, the cyclophilin inhibitor is selected from: OCB-030 (NVP-018), SCY-635, SCY-575 and CPI-431-32.

[0054] Preferably, said HBV polymerase inhibitor is selected from: entecavir (Baraclude, Entavir), lamivudine (3TC, Zeffix, Heptovir, Epivir, and Epivir-HBV), telbivudine (Tyzeka, Sebivo), clevudine, besifovir, adefovir (hepsera), tenofovir. Preferably, tenofovir is in a salt form. Preferably, tenofovir is in a salt form selected from: tenofovir disoproxil fumarate

(Viread), tenofovir alafenamide fumarate (TAF), tenofovir disoproxil orotate (DA-2802), tenofovir disopropxil aspartate (CKD-390), AGX-1009, and CMX157.

[0055] Preferably, the dinucleotide is SB9200. Preferably, the SMAC inhibitor is Birinapant. Preferably, the HDV targeting agent is Lonafamib.

[0056] Preferably, the HBV RNA destabilizer or other small-molecule inhibitor of HBV protein expression is RG7834 or AB-452.

[0057] Preferably, the at least one further therapeutic agent is an agent useful in the treatment and prevetion of hepatitis B. Preferably, the at least one further therapeutic agent is an anti-HDV agent, an anti-HCV agent and/or an anti-HIV agent.

[0058] Preferably, the at least one further therapeutic agent is selected from the group consisting of: HBV polymerase inhibitor, interferon, viral entry inhibitor, BAY 41-4109, reverse transcriptase inhibitor, a TLR-agonist, AT-61 ((E)-N-(1-chloro-3-oxo-1-phenyl-3-(piperidin-1-yl)prop-1-en-2-yl)benzamide), AT-130 ((E)-N-(1-bromo-1-(2-methoxyphenyl)-3-oxo-3-(piperidin-1-yl)prop-1-en-2-yl)-4-nitrobenzamide), and a combination thereof, wherein the HBV polymerase inhibitor is preferably at least one of Lamivudine, Entecavir, Tenofovir, Adefovir, Telbivudine, Clevudine; and wherein the TLR agonist is preferably selected from the group consisting of SM360320 (9-benzyl-8-hydroxy-2-(2-methoxy-ethoxy)adenine), AZD 8848 (methyl [3-({[3-(6-amino-2-butoxy-8-oxo-7,8-dihydro-9H-purin-9-yl)propyl][3-(4-morpholinyl)propyl] amino }methyl)phenyl] acetate) and a combination thereof.

[0059] Preferably, the compound of the invention is for use in combination with one, two or more further therapeutic agent(s) as defined above.

[0060] Preferably, the pharmaceutical composition of the invention comprises one, two or more further therapeutic agent(s) as defined above.

[0061] Preferably, said pharmaceutical composition is for use in the treatment and/or prevention of a HBV infection. Even more preferably, said pharmaceutical composition is for use in treating, eradicating, reducing, slowing or inhibiting an HBV infection in an individual in need thereof, and/or in reducing the viral load associated with an HBV infection in an individual in need thereof, and/or reducing reoccurrence of an HBV infection in an individual in need thereof, and/or inducing remission of hepatic injury from an HBV infection in an individual in need thereof, and/or prophylactically treating an HBV infection in an individual afflicted with a latent HBV infection. In an embodiment, the invention provides a kit comprising at least one pharmaceutically acceptable vial or container containing one or more doses of a compound of the invention or of a pharmaceutical composition of the invention and optionally a) instructions for use thereof in mammals and/or b) an infusion bag or container containing a pharmaceutically acceptable diluent. It is a further object of the invention a process for the synthesis of a compound of general formula (I), (Ia) or (Ib) according to the synthetic Schemes included in the description of the invention.

[0062] It is a further object of the invention a pharmaceutical composition comprising an effective amount of one or more compounds as defined above or a pharmaceutically acceptable prodrug thereof, alone or in combination with other active compounds, and at least one pharmaceutically acceptable excipient.

[0063] In a preferred embodiment, the invention relates to compounds of formula (I) wherein Cy is phenyl. Still preferably, the invention relates to compounds of formula (I) wherein X is O.

[0064] In a preferred embodiment, the compound of the invention has formula (Ia) wherein Cy is phenyl, X is O or NH, A is CH_2, R_1 is CH_3, R_2 and R_3 are hydrogen.

[0065] In a further preferred embodiment, the compound of the invention has formula (Ib) wherein Cy is phenyl, X is O, Y is a single bond, Y' is CH_2, Y" is CH_2 or a single bond and A is CH_2, O or N-R_6.

[0066] The present invention includes within its scope prodrugs of the compounds of formula (I), (Ia) or (Ib) above. In general, such prodrugs will be functional derivatives of the compounds of formula (I), (Ia), (Ib) which are readily convertible *in vivo* into the required compound of formula (I), (Ia), (Ib). Conventional procedures for the selection and preparation of suitable prodrug derivatives are described, for example, in "Design of Prodrugs", ed. H. Bundgaard, Elsevier, 1985.

[0067] A prodrug may be a pharmacologically inactive derivative of a biologically active substance (the "parent drug" or "parent molecule") that requires transformation within the body in order to release the active drug, and that has improved delivery properties over the parent drug molecule. The transformation *in vivo* may be, for example, as the result of some metabolic process, such as chemical or enzymatic hydrolysis of a carboxylic, phosphoric or sulphate ester, or reduction or oxidation of a susceptible functionality.

[0068] The disclosure also includes all suitable isotopic variations of a compound of the disclosure. Examples of isotopes that can be incorporated into compounds of the disclosure include isotopes such as ^{2}H, ^{3}H, ^{13}C, ^{14}C, ^{15}N, ^{17}O, ^{18}O, ^{31}P, ^{32}P, ^{35}S, ^{18}F and ^{36}Cl, respectively. Certain isotopic variations of the disclosure, for example, those in which a radioactive isotope such as ^{3}H or ^{14}C is incorporated, are useful in drug and/or substrate tissue distribution studies. Further, substitution with isotopes such as deuterium ^{2}H, may afford certain therapeutic advantages resulting from greater metabolic stability. Isotopic variations of the compounds of the disclosure can generally be prepared by conventional procedures such as by the illustrative methods or by the preparations described in the examples hereafter using appropriate isotopic variations of suitable reagents. The present invention includes within its scope solvates of the compounds of (I), (Ia) or (Ib) and salts thereof, for example, hydrates.

[0069] The compounds of the present invention may have asymmetric centers, chiral axes, and chiral planes (as described in: E.L. Eliel and S.H. Wilen, Stereochemistry of Carbon Compounds, John Wiley & Sons, New York, 1994, pages 1119-1190), and occur as racemates, racemic mixtures, and as individual diastereomers, with all possible isomers and mixtures thereof, including optical isomers, all such stereoisomers being included in the present invention. In addition, the compounds disclosed herein may exist as tautomers and both tautomeric forms are intended to be encompassed by the scope of the invention, even though only one tautomeric structure is depicted. The compounds may exist in different isomeric forms, all of which are encompassed by the present invention.

[0070] Pure stereoisomeric forms of the compounds and intermediates of this invention may be obtained by the application of art-known procedures. For instance, enantiomers may be separated from each other by the selective crystallization of their diastereomeric salts or by chromatographic techniques using chiral stationary phases. Pure stereochemically isomeric forms may also be derived from the corresponding pure stereochemically isomeric forms of the appropriate starting materials, provided that the reaction occurs stereospecifically.

[0071] When any variable (e.g. R_1 and R_2, etc.) occurs more than one time in any constituent, its definition on each occurrence is independent at every other occurrence. Also, combinations of substituents and variables are permissible only if such combinations result in stable compounds. Lines drawn into the ring systems from substituents represent that the indicated bond may be attached to any of the substitutable ring atoms. If the ring system is polycyclic, it is intended that the bond be attached to any of the suitable carbon atoms on the proximal ring only.

[0072] It is understood that substituents and substitution patterns on the compounds of the instant invention can be selected by one of ordinary skill in the art to provide compounds that are chemically stable and that can be readily synthesized by techniques known in the art, as well as those methods set forth below, from readily available starting materials. If a substituent is itself substituted with more than one group, it is understood that these multiple groups may be on the same carbon or on different carbons, so long as a stable structure results. The phrase "optionally substituted" should be taken to be equivalent to the phrase "unsubstituted or substituted with one or more substituents" and in such cases the preferred embodiment will have from zero to three substituents. More particularly, there are zero to two substituents.

[0073] The expressions "one or more substituents" and "one, two or more substituents" refer to in particular to 1, 2, 3, 4 or more substituents, in particular to 1, 2, 3 or 4 substituents, more in particular 1, 2 or 3 substituents.

[0074] As used herein "Y is a single bond" indicates that, in the general formula (I), X is directly linked via a single bond to the carbon atom bearing R_2; "Y' is a single bond" indicates that, in the general formula (I), A is directly linked via a single bond to Z; "Y" is a single bond" indicates that, in the general formula (I), A is directly linked via a single bond to the carbon atom bearing R_2; "Y"' is a single bond" indicates that Z, in the general formula (I), is directly linked via a single bond to the carbon atom bearing R_2.

[0075] As used herein, "alkyl" is intended to include both branched and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms. For example, "C_{1-6}alkyl" is defined to include groups having 1, 2, 3, 4, 5 or 6 carbons in a linear or branched arrangement. For example, "C_{1-6} alkyl" specifically includes methyl, ethyl, *n*-propyl, *i*-propyl, *n*-butyl, *t*-butyl, *i*-butyl, pentyl, hexyl, and so on. "C_{1-4}alkyl" is defined to include groups having 1, 2, 3 or 4 carbons in a linear or branched arrangement. For example, "C_{1-4} alkyl" specifically includes methyl, ethyl, *n*-propyl, *i*-propyl, *n*-butyl, *t*-butyl, *i*-butyl, and so on. "C_{1-3}alkyl" is defined to include groups having 1, 2, or 3 carbons in a linear or branched arrangement. For example, "C_{1-3} alkyl" specifically includes methyl, ethyl, *n*-propyl, *i*-propyl, and so on. Preferred alkyl groups are methyl, ethyl, *i*-propyl or *t*-butyl.

[0076] As used herein, "alkoxy" represents an alkyl group of indicated number of carbon atoms attached through an oxygen bridge. "Alkoxy" therefore encompasses the definitions of alkyl above. C_{1-6} alkoxy group is preferably a linear or branched C_{1-4} alkoxy group, more preferably a C_{1-3}alkoxy group, still more preferably a C_{1-2} alkoxy group. Examples of suitable alkoxy groups include, but are not limited to methoxy, ethoxy, *n*-propoxy, *i*-propoxy, *n*-butoxy, *s*-butoxy or *t*-butoxy. preferred alkoxy groups include methoxy, ethoxy and *t*-butoxy.

[0077] As used herein, the terms "haloC_{1-6}alkyl" and "haloC_{1-6}alkoxy" mean a C_{1-6}alkyl or C_{1-6}alkoxy group in which one or more (in particular, 1 to 3) hydrogen atoms have been replaced by halogen atoms, especially fluorine or chlorine atoms. HaloC_{1-6}alkoxy group is preferably a linear or branched haloC_{1-4}alkoxy group, more preferably a haloC_{1-3}alkoxy group, still more preferably a haloC_{1-2}alkoxy group, for example OCF_3, $OCHF_2$, OCH_2F, OCH_2CH_2F, OCH_2CHF_2 or OCH_2CF_3, and most especially OCF_3 or $OCHF_2$. HaloC_{1-6}alkyl group is preferably a linear or branched haloC_{1-3}alkyl group, more preferably a haloC_{1-2}alkyl group for example, CF_3, CHF_2, CH_2F, CH_2CH_2F, CH_2CHF_2, CH_2CF_3 or $CH(CH_3)CF_3$, and most especially CF_3, CHF_2 or $CH(CH_3)CF_3$,.

[0078] As used herein, the term "hydroxyC_{1-6}alkyl" means a C_{1-6}alkyl group in which one or more (in particular, 1 to 3) hydrogen atoms have been replaced by hydroxy groups. Similarly, the term "hydroxyC_{1-4}alkyl" means a C_{1-4}alkyl group in which one or more (in particular, 1 to 2) hydrogen atoms have been replaced by hydroxy groups. Illustrative examples include, but are not limited to CH_2OH, CH_2CH_2OH, $CH(CH)_3OH$ and $CHOHCH_2OH$.

[0079] As used herein, the term "aryl" means a monocyclic or polycyclic aromatic ring comprising carbon atoms and hydrogen atoms. If indicated, such aromatic ring may include one or more heteroatoms, then also referred to as "het-

eroaryl", preferably, 1 to 3 heteroatoms, independently selected from nitrogen, oxygen, and sulfur, preferably nitrogen. As is well known to those skilled in the art, heteroaryl rings have less aromatic character than their all-carbon counter parts. Thus, for the purposes of the present invention, a heteroaryl group need only have some degree of aromatic character. Illustrative examples of aryl groups are optionally substituted phenyl. Illustrative examples of heteroaryl groups according to the invention include optionally substituted thiophene, oxazole, thiazole, thiadiazole, imidazole, pyrazole, pyrimidine, pyrazine and pyridine. Thus, examples of monocyclic aryl optionally containing one or more heteroatoms, for example one or two heteroatoms, are a 5- or 6-membered aryl or heteroaryl group such as, but not limited to, phenyl, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, pyrrolyl, thienyl, thiazolyl, thiadiazolyl, pyrazolyl, imidazolyl, triazolyl, tetrazolyl, furyl, isoxazolyl, oxadiazolyl and oxazolyl. Examples of polycyclic aromatic ring, optionally containing one or more heteroatoms, for example one or two heteroatoms, are a 8-10 membered aryl or heteroaryl group such as, but not limited to, benzimidazolyl, benzofurandionyl, benzofuranyl, benzofurazanyl, benzopyrazolyl, benzotriazolyl, benzothienyl, benzoxazolyl, benzoxazolonyl, benzothiazolyl, benzothiadiazolyl, benzodioxolyl, benzoxadiazolyl, benzoisoxazolyl, benzoisothiazolyl, indolyl, indolizinyl, isoindolinyl, indazolyl, isobenzofuranyl, isoindolyl, isoquinolyl, quinazolinyl, quinolyl, quinoxalinyl, quinolizinyl, naphtyl, naphthyridinyl and phthalazinyl. A preferred aromatic ring according to the present invention is phenyl. A preferred heteroaryl according to the present invention is pyridyl.

[0080] Heterocycle, heterocyclic compound or ring structure is a cyclic compound that has atoms of at least two different elements as members of its ring(s).

[0081] As used herein, the term "heterocyclic ring" is a saturated or partially saturated non aromatic monocyclic or bicyclic ring system, of 4 to 10 members which contains one or more heteroatoms selected from N, O or S. Examples include, but are not limited to azetidinyl, piperazinyl, piperidinyl, morpholinyl, thiomorpholinyl, thiazolidinyl, pyrrolidinyl, azepanyl, diazepanyl, oxazepanyl, thiazepanyl, azocanyl, oxazocanyl and the hexahydrofuro[2,3-b]furan system.

[0082] A substituent on a saturated, partially saturated or unsaturated heterocycle can be attached at any substitutable position.

[0083] As used herein, the term "C_{1-6} alkanediyl" as group or part of a group defines bivalent straight or branched chained saturated hydrocarbon radicals having from 1 to 4 carbon atoms. C_{1-6} alkanediyl group, is preferably a C_{1-4} alkanediyl group, a C_{1-3} alkanediyl or more preferably a C_{1-2} alkanediyl. Examples include, but are not limited to methanediyl, ethanediyl, propanediyl, butanediyl, pentanediyl and hexanediyl. Preferred are methanediyl, ethanediyl and propanediyl.

[0084] As used herein, the term "3-7 membered saturated ring" means saturated cyclic hydrocarbon (cycloalkyl) with 3 or 4, 5, 6 or 7 carbon atoms and is generic to cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl. Said saturated ring optionally contains one or more heteroatoms (also referred to as heterocyclyl or heterocyclic ring), such that at least one carbon atom is replaced by a heteroatom selected from N, O and S, in particular from N and O. Examples include, but are not limited to oxetanyl, azetidinyl, tetrahydro-2H-pyranyl, piperazinyl, piperidinyl, tetrahydrofuranyl, morpholinyl, thiomorpholinyl, thiazolidinyl, thiolane 1,1-dioxide, pyrrolidinyl, azepanyl, diazepanyl, oxazepanyl, thiazepanyl, azocanyl or oxazocanyl. Preferred are saturated cyclic hydrocarbons with 3 or 4 carbon atoms and 1 oxygen or 1 nitrogen atom. Examples include oxetanyl, tetrahydrofuranyl, tetrahydro-2H-pyranyl, piperidinyl or pyrrolidinyl. It should be noted that different isomers of the various heterocycles may exist within the definitions as used throughout the specification. For example, pyrrolyl may be 1H-pyrrolyl or 2H-pyrrolyl.

[0085] It should also be noted that the radical positions on any molecular moiety used in the definitions may be anywhere on such moiety as long as it is chemically stable. For example, pyridyl includes 2-pyridyl, 3-pyridyl, 4-pyridyl.

[0086] As used herein, the term "halogen" refers to fluorine, chlorine, bromine and iodine, of which fluorine, chlorine and bromine are preferred.

[0087] The term "heteroatom" refers to an atom other than carbon or hydrogen in a ring structure or a saturated backbone as defined herein. Typical heteroatoms include N(H), O, S.

[0088] As used herein, the term "C_{3-8} cycloalkyl" means saturated cyclic hydrocarbon (cycloalkyl) with 3 or 4, 5, 6, 7 or 8 carbon atoms and is generic to cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl or cyclooctyl.

[0089] The term "C_{1-6}alkylaryl" as used herein indicates one or more aryl groups appended to a C_{1-6}alkyl radical. As used herein, the term "C_{1-6}alkylheteroaryl" indicates one or more heteroaryl groups appended to a C_{1-6}alkyl radical. As used herein, the term "C_{1-6}alkyl-C_{3-8}cycloalkyl" indicates one or more C_{3-8}cycloalkyl groups appended to a C_{1-6}alkyl radical.

[0090] The terms "spiro-C_{3-8}cycloalkyl" or "spiro-C_{3-8}heterocycloalkyl" indicate respectively a C_{3-}scycloalkyl or a C_{3-8}heterocycloalkyl forming a bicyclic organic compound with rings connected through just one atom. The rings can be different in nature or identical. The connecting atom is also called the spiroatom, most often a quaternary carbon ("spiro carbon").

[0091] Included in the instant invention is the free base of compounds of formula (I), (Ia) or (Ib) as well as the pharmaceutically acceptable salts and stereoisomers thereof. Some of the specific compounds exemplified herein are the protonated salts of amine compounds. Compounds of formula (I), (Ia) or (Ib) containing one or more N atoms may be protonated on any one, some or all of the N atoms. The term "free base" refers to the amine compounds in non-salt

form. The encompassed pharmaceutically acceptable salts not only include the salts exemplified for the specific compounds described herein, but also all the typical pharmaceutically acceptable salts of the free form of compounds of formula (I), (Ia) or (Ib).The free form of the specific salt compounds described may be isolated using techniques known in the art. For example, the free form may be regenerated by treating the salt with a suitable dilute aqueous base solution such as dilute aqueous NaOH, potassium carbonate, ammonia and sodium bicarbonate. The free forms may differ from their respective salt forms somewhat in certain physical properties, such as solubility in polar solvents, but the acid and base salts are otherwise pharmaceutically equivalent to their respective free forms for purposes of the invention.

[0092] The pharmaceutically acceptable salts of the instant compounds can be synthesized from the compounds of this invention which contain a basic or acidic moiety by conventional chemical methods. Generally, the salts of the basic compounds are prepared either by ion exchange chromatography or by reacting the free base with stoichiometric amounts or with an excess of the desired salt-forming inorganic or organic acid in a suitable solvent or various combinations of solvents. Similarly, the salts of the acidic compounds are formed by reactions with the appropriate inorganic or organic base.

[0093] Thus, pharmaceutically acceptable salts of the compounds of this invention include the conventional non-toxic salts of the compounds of this invention as formed by reacting a basic instant compound with an inorganic or organic acid. For example, conventional non-toxic salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, nitric and the like, as well as salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pamoic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, sulfanilic, 2-acetoxy-benzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, isethionic, trifluoroacetic and the like. Preferably, a pharmaceutically acceptable salt of this invention contains one equivalent of a compound of formula (I), (Ia) or (Ib) and 1, 2 or 3 equivalent of an inorganic or organic acid. More particularly, pharmaceutically acceptable salts of this invention are the tartrate, trifluoroacetate or the chloride salts.

[0094] When the compound of the present invention is acidic, suitable "pharmaceutically acceptable salts" refers to salts prepared form pharmaceutically acceptable non-toxic bases including inorganic bases and organic bases. Salts derived from inorganic bases include aluminum, ammonium, calcium, copper, ferric, ferrous, lithium, magnesium, manganic salts, manganous, potassium, sodium, zinc and the like. Particularly preferred are the ammonium, calcium, magnesium, potassium and sodium salts. Salts derived from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines and basic ion exchange resins, such as arginine, betaine caffeine, choline, N,N^1-dibenzylethylenediamine, diethylamin, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethylmorpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine tripropylamine, tromethamine and the like.

[0095] The preparation of the pharmaceutically acceptable salts described above and other typical pharmaceutically acceptable salts is more fully described by Berg et al., "Pharmaceutical Salts," J. Pharm. Sci., 1977:66:1-19.

[0096] It will also be noted that the compounds of the present invention are potentially internal salts or zwitterions, since under physiological conditions a deprotonated acidic moiety in the compound, such as a carboxyl group, may be anionic, and this electronic charge might then be balanced off internally against the cationic charge of a protonated or alkylated basic moiety, such as a quaternary nitrogen atom.

[0097] The compounds of the present invention find use in a variety of applications for human and animal health. The compounds of the present invention are inhibitors of hepatitis B virus (HBV). The compounds of the present invention are inhibitors of hepatitis B virus (HBV) useful for the treatment and/or prevention of HBV infection. In particular the compounds of the present invention are inhibitors of hepatitis B virus (HBV) core (HBc) protein useful for the treatment and/or prevention of a HBV infection.

[0098] The compounds, compositions and methods provided herein are particularly deemed useful for treating, ameliorating or preventing HBV infection and related conditions, including chronic hepatitis B, HBV/HDV co-infection, HBV/HCV co-infection, HBV/HIV co-infection.

[0099] In the present invention, the expression "HBV infection" comprises any and all conditions deriving from infection with HBV, including but not limited to hepatitis B, preferably chronic hepatitis B, HBV/HDV co-infection, HBV/HCV coinfection, HBV/HIV coinfection.

[0100] The compounds of this invention may be administered to mammals, preferably humans, either alone or in combination with pharmaceutically acceptable carriers, excipients or diluents, in a pharmaceutical composition, according to standard pharmaceutical practice. In one embodiment, the compounds of this invention may be administered to animals. The compounds can be administered orally or parenterally, including the intravenous, intramuscular, intraperitoneal, subcutaneous, rectal and topical routes of administration.

[0101] The invention also provides pharmaceutical compositions comprising one or more compounds of this invention and a pharmaceutically acceptable carrier. The pharmaceutical compositions containing the active ingredient may be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible

powders or granules, emulsions, hard or soft capsules, or syrups or elixirs. Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. These excipients may be for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, microcrystalline cellulose, sodium crosscarmellose, corn starch, or alginic acid; binding agents, for example starch, gelatin, polyvinyl-pyrrolidone or acacia, and lubricating agents, for example, magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to mask the unpleasant taste of the drug or delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a water soluble taste masking material such as hydroxypropyl-methylcellulose or hydroxypropylcellulose, or a time delay material such as ethyl cellulose, cellulose acetate butyrate may be employed.

[0102] Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water soluble carrier such as polyethyleneglycol or an oil medium, for example peanut oil, liquid paraffin, or olive oil.

[0103] Aqueous suspensions contain the active material in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethyl-cellulose, sodium alginate, polyvinyl-pyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may be a naturally-occurring phosphatide, for example lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives, for example ethyl, or n-propyl p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents, and one or more sweetening agents, such as sucrose, saccharin or aspartame.

[0104] Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set forth above, and flavoring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an anti-oxidant such as butylated hydroxyanisol or alpha-tocopherol.

[0105] Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example sweetening, flavoring and coloring agents, may also be present. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

[0106] The pharmaceutical compositions of the invention may also be in the form of an oil-in-water emulsions. The oily phase may be a vegetable oil, for example olive oil or arachis oil, or a mineral oil, for example liquid paraffin or mixtures of these. Suitable emulsifying agents may be naturally occurring phosphatides, for example soy bean lecithin, and esters or partial esters derived from fatty acids and hexitol anhydrides, for example sorbitan monooleate, and condensation products of the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening, flavoring agents, preservatives and antioxidants. Syrups and elixirs may be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative, flavoring and coloring agents and antioxidant.

[0107] The pharmaceutical compositions may be in the form of a sterile injectable aqueous solutions. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution.

[0108] The sterile injectable preparation may also be a sterile injectable oil-in-water microemulsion where the active ingredient is dissolved in the oily phase. For example, the active ingredient may be first dissolved in a mixture of soybean oil and lecithin. The oil solution then introduced into a water and glycerol mixture and processed to form a microemulstion.

[0109] The injectable solutions or microemulsions may be introduced into a patient's blood stream by local bolus injection. Alternatively, it may be advantageous to administer the solution or microemulsion in such a way as to maintain a constant circulating concentration of the instant compound. In order to maintain such a constant concentration, a continuous intravenous delivery device may be utilized. An example of such a device is the Deltec CADD-PLUS™ model 5400 intravenous pump.

[0110] The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleagenous suspension for intramuscular and subcutaneous administration. This suspension may be formulated according to the known art

using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally acceptable diluent or solvent, for example as a solution in 1,3-butanediol. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

[0111] Compounds of formula (I), (Ia) or (Ib) may also be administered in the form of suppositories for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials include cocoa butter, glycerinated gelatin, hydrogenated vegetable oils, mixtures of polyethylene glycols of various molecular weights and fatty acid esters of polyethylene glycol.

[0112] For topical use, creams, ointments, jellies, solutions or suspensions, etc., containing the compound of formula (I), (Ia) or (Ib) are employed. (For purposes of this application, topical application shall include mouth washes and gargles.)

[0113] The compounds for the present invention can be administered in intranasal form via topical use of suitable intranasal vehicles and delivery devices, or via transdermal routes, using those forms of transdermal skin patches well known to those of ordinary skill in the art. To be administered in the form of a transdermal delivery system, the dosage administration will, of course, be continuous rather than intermittent throughout the dosage regimen. Compounds of the present invention may also be delivered as a suppository employing bases such as cocoa butter, glycerinated gelatin, hydrogenated vegetable oils, mixtures of polyethylene glycols of various molecular weights and fatty acid esters of polyethylene glycol.

[0114] When a compound according to this invention is administered into a human subject, the daily dosage will normally be determined by the prescribing physician with the dosage generally varying according to the age, weight, sex and response of the individual patient, as well as the severity of the patient's symptoms.

[0115] In one exemplary application, a suitable amount of compound is administered to a mammal undergoing anti HBV treatment. Administration generally occurs in an amount between about: 0.01 mg/kg of body weight to about 60 mg/kg of body weight per day, preferably of between 0,5 mg/kg of body weight to about 40 mg/kg of body weight per day.

[0116] The instant compounds are also useful in combination with known therapeutic agents for simultaneous, separate or sequential administration.

[0117] In an embodiment, the compounds of the present invention may be used in combination with at least one or more additional therapeutic agents, in particular anti-HBV agents.

[0118] The indication that compounds of the invention are for use in the treatment and/or prevention of a HBV infection indicates that the compounds are efficacious for treating, eradicating, reducing, slowing or inhibiting an HBV infection.

[0119] The term "anti-HBV agent", or more simply "HBV antiviral(s)" also includes compounds that are therapeutic nucleic acids, antibodies or proteins either in their natural form or chemically modified and/or stabilized. The term therapeutic nucleic acid includes but is not limited to nucleotides and nucleosides, oligonucleotides, polynucleotides, of which non limiting examples are antisense oligonucleotides, miRNA, siRNA, shRNA, therapeutic vectors and DNA/RNA editing components.

[0120] The term anti-HBV agent also includes compounds capable of treating HBV infection via immunomodulation, i.e. immunomodulators or immunomodulating compounds. Examples of immunomodulators are interferon-α (IFN-α), pegylated interferon-α or stimulants of the innate immune system such as Toll-like receptor 7 and/or 8 agonists and therapeutic or prophylactic vaccines. One embodiment of the present invention relates to combinations of a compound of formula (I) or (Ia) or any subgroup thereof, as specified herein, with an immunomodulating compound, more specifically a Toll-like receptor 7 and/or 8 agonist.

[0121] The additional HBV antiviral(s) can be selected for example, from therapeutic vaccines; RNA interference therapeutic/antisense oligonucleotides (e.g. siRNA, ddRNA, shRNA); immunomodulators (such as TLR agonists (e.g. TLR7, TLR8 or TLR9 agonists); STING agonists; RIG-I modulators; NKT modulators; IL agonists; Interleukin or other immune active proteins, therapeutic and prophylactic vaccines and immune checkpoint modulators; HBV entry inhibitors; cccDNA modulators (such as for example direct cccDNA inhibitors, inhibtors of cccDNA formation or maintenance, cccDNA epigenetic modifiers, inhibitors of cccDNA transcription); inhibitors of HBV protein espression; agents targeting HBV RNA; capsid assembly inhibitors/modulators; core or X protein targeting agents; nucleotide analogues; nucleoside analogues; interferons or modified interferons; HBV antivirals of distinct or unknown mechanism; cyclophilin inhibitors; sAg release inhibitors; HBV polymerase inhibitors; dinucleotides; SMAC inhibitors; HDV targeting agents; viral maturation inhibitors; reverse transcriptase inhibitors and HBV RNA destabilizers and other small-molecule inhibitors of HBV protein expression.

[0122] In particular, the combination of previously known anti-HBV agents, such as interferon-α (IFN-α), pegylated interferon-α, 3TC, tenofovir, lamivudine, entecavir, telbivudine, and adefovir or a combination thereof, and a compound of formula (I) or (Ia) or any subgroup thereof can be used as a medicine in a combination therapy. Additional examples of further therapeutic agents that may be combined with the compounds of the present invention include: Zidovudine, Didanosine, Zalcitabine, Stavudine, Abacavir, ddA Emtricitabine, Apricitabine, Atevirapine, ribavirin, acyclovir, valacy-

clovir, famciclovir, ganciclovir, valganciclovir, cidofovir, Efavirenz, Nevirapine, Delavirdine and Etravirine.

[0123] Particular examples of such HBV antiviral(s) include, but are not limited to:

- RNA interference (RNAi) therapeutics: TKM-HBV (also known as ARB-1467), ARB-1740, ARC-520, ARC-521, BB-HB-331, REP-2139, ALN-HBV, ALN-PDL, LUNAR-HBV, GS3228836, and GS3389404;
- HBV entry inhibitors: Myrcludex B, IVIG-Tonrol, GC-1102;
- HBV capsid inhibitor/modulators, core or X protein targeting agents, direct cccDNA inhibitors, inhibitors of cccDNA formation or maintenance, or cccDNA epigenetic modifiers: BAY 41-4109, NVR 3-778, GLS-4, NZ-4 (also known as W28F), Y101, ARB-423, ARB-199, ARB-596, AB-506, JNJ-56136379, ASMB-101 (also known as AB-V102), ASMB-103, CHR-101, CC-31326, AT-130, RO7049389.
- HBV polymerase inhibitors: entecavir (Baraclude, Entavir), lamivudine (3TC, Zeffix, Heptovir, Epivir, and Epivir-HBV), telbivudine (Tyzeka, Sebivo), clevudine, besifovir, adefovir (hepsera), tenofovir (in particular tenofovir disoproxil fumarate (Viread), tenofovir alafenamide fumarate (TAF)), tenofovir disoproxil orotate (also known as DA-2802), tenofovir disopropxil aspartate (also known as CKD-390), AGX-1009, and CMX157);
- HBV RNA destabilizers and other small-molecule inhibitors of HBV protein expression: RG7834, AB-452;
- cyclophilin inhibitors: OCB-030 (also known as NVP-018), SCY-635, SCY-575, and CPI-431-32;
- dinucleotides: SB9200;
- compounds of distinct or unknown mechanism, such as but not limited to AT-61 ((E)-N-(1-chloro-3-oxo-1-phenyl-3-(piperidin-1-yl)prop-1-en-2-yl)benzamide), AT130 ((E)-N-(1-bromo-1-(2-methoxyphenyl)-3-oxo-3-(piperidin-1-yl)prop-1-en-2-yl)-4-nitrobenzamide), and similar analogs; REP-9AC (also known as REP-2055), REP-9AC' (also known as REP-2139), REP-2165 and HBV-0259;
- TLR agonists (TLR7, 8 and/or 9): RG7795 (also known as RO-6864018), GS-9620, SM360320 (9-benzyl-8-hydroxy-2-(2-methoxy-ethoxy)adenine) and AZD 8848 (methyl [3-({[3-(6-amino-2-butoxy-8-oxo-7,8-dihydro-9H-pyrin-9-yl)propyl][3-(4-morpholinyl)propyl]amino}methyl)phenyl]acetate); ARB- 1598;
- RIG-I modulators: SB-9200;
- SMAC inhibitor: Birinapant
- Immune Check Point inhibitors: BMS-936558 (Opdivo (nivolumab)), KEYTRUDA® (pembrolizumab);
- therapeutic vaccines: HBsAG-HBIG, HB-Vac, ABX203, NASVAC, GS-4774, GX- 110 (also known as HB-110E), CVI-HBV-002, RG7944 (also known as INO-1800), TG-1050, FP-02 (Hepsyn-B), AIC649, VGX-6200, KW-2, TomegaVax-HBV, ISA-204, NU-500, INX-102-00557 HBV MVA, PepTcell;
- IL agonists and immune acting proteins: INO-9112; recombinant IL12;
- interferons: interferon alpha (IFN-α), interferon alpha-2a, recombinant interferon alpha-2a, peginterferon alpha-2a (Pegasys), interferon alpha-2b (Intron A), recombinant interferon alpha-2b, interferon alpha-2b XL, peginterferon alpha-2b, glycosylated interferon alpha-2b, interferon alpha-2c, recombinant interferon alpha-2c, interferon beta, interferon beta- la, peginterferon beta-la, interferon delta, interferon lambda (IFN-λ), peginterferon lambda-1, interferon omega, interferon tau, interferon gamma (IFN-γ), interferon alfacon-1, interferon alpha-nl, interferon alpha-n3, albinterferon alpha-2b, BLX-883, DA-3021, PI 101 (also known as AOP2014), PEG-infergen, Belerofon, INTEFEN-IFN, albumin/interferon alpha 2a fusion protein, rHSA-IFN alpha 2a, rHSA-IFN alpha 2b, PEG-IFN-SA, interferon alpha biobetter; in particular, peginterferon alpha-2a, peginterferon alpha-2b, glycosylated interferon alpha-2b, peginterferon beta-la, and peginterferon lambda-1; more in particular, peginterferon alpha-2a;
- HDV targeting agent: Lonafamib.

[0124] The term "administration" and variants thereof (e.g., "administering" a compound) in reference to a compound of the invention means introducing the compound or a prodrug of the compound into the system of the animal in need of treatment. When a compound of the invention or prodrug thereof is provided in combination with one or more other active agents (e.g., a cytotoxic agent, etc.), "administration" and its variants are each understood to include concurrent and sequential introduction of the compound or prodrug thereof and other agents.

[0125] In some embodiments, pulsed administration is more effective than continuous treatment because total pulsed doses are often lower than would be expected from continuous administration of the same composition. Each pulse dose can be reduced and the total amount of drug administered over the course of treatment is minimized. Individual pulses can be delivered to the patient continuously over a period of several hours, such as about 2, 4, 6, 8, 10, 12, 14 or 16 hours, or several days, such as 2, 3, 4, 5, 6 or 7 days.

[0126] As used herein, the term "composition" is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combination of the specified ingredients in the specified amounts.

[0127] The term "therapeutically effective amount" as used herein means that amount of active compound or pharmaceutical agent that elicits the biological or medicinal response in a tissue, system, animal or human that is being sought by a researcher, veterinarian, medical doctor or other clinician. The present invention will be described by means

of the following non-limiting examples and biological data are presented.

MATERIALS AND METHODS

Chemistry

General

[0128] Unless otherwise indicated, commercially available reagents and solvents (HPLC grade) were used without further purification.

[0129] Specifically, the following abbreviations may have been used in the descriptions of the experimental methods:

NMR: Nuclear Magnetic Resonance; ^{1}H: proton; MHz: Megahertz; Hz: Hertz; HPLC: High Performance Liquid Chromatography; LC-MS: Liquid Chromatography Mass Chromatography Spectrum; s: second(s); min: minute(s); h: hour(s); mg: milligram(s); g: gram(s); M1: microliter(s);
mL: millilitre(s); mmol: millimole(s); nm: nanometer(s) μM: micromolar; M: molarity or molar concentration; Rt: retention time in minutes; MW: microwave; Boc: *tert*-butyloxycarbonyl protecting group; DMF: dimethylformamide; DMSO: dimethylsulfoxide; MeOH: methanol;
EtOH: ethanol; EtOAc: ethyl acetate; DCM: dichloromethane; MeCN: Acetonitrile; PE: Petroleum Ether; TFA: trifluoroacetic acid; (g): gas; eq.: equivalent(s);; RT: room temperature;
DIPEA: *N,N*-diisopropylethylamine; DIAD: Diisopropyl azodicarboxylate; sat.aq.: saturated aqueous solution; TEA: triethylamine; THF: tetrahydrofuran; IPA: isopropylamine.; *p*TSA: para toluene sulfonic acid; TBDMS: *tert*-butyldimethylsilyl; LiHMDS: Lithium bis(trimehtylsilyl)amide; TBTU: 2-(1H-Benzotriazole-1-yl)-1,1,3,3-tetramethylaminium tetrafluoroborate;

[0130] Except where indicated otherwise, all temperatures are expressed in °C (degrees centigrade) or K (Kelvin).

[0131] The ^{1}H-NMR spectra were acquired with an Avance II 300 MHz Bruker spectrometer. The chemical shifts are expressed in parts per million (ppm, δ units). The coupling constants are expressed in Hertz (Hz) and the splitting patterns are described as s (singlet), bs (broad signal), d (doublet), t (triplet), q (quartet), quint (quintet), m (multiplet).

[0132] The LC-MS analyses were performed by means of an UPLC Acquity Waters System equipped with the SQD spectrometer, single quadrupole mass detector, and a TUV detector, using column 1: ACQUITY UPLC BEH SHIELD, RP_{18} (2.1x50mm, id=1.7 μm); column2: ACQUITY UPLC HSS T3, RP_{18} (2.1x50mm, id=1.8 μm) and column3: ACQUITY UPLC BEH SHIELD, RP_{18} (2.1x100mm, id=1.7 μm). Column temperature 40°C. Sample temperature 25°C. Phase A was composed by water (HiPerSolv Chromanorm Water VWR for HPLC-MS) + 0,05% Trifluoroacetic Acid; Phase B by CH_3CN (HiPerSolv Chromanorm Acetonitrile SuperGradient VWR, suitable for UPLC/UHPLC instruments) + 0,05% Trifluoroacetic Acid; flow rate: 0,5 mL/min; UV detection (DIODE array) 200 nm; ESI+ and ESI- detection in the 100-1000 m/z range.

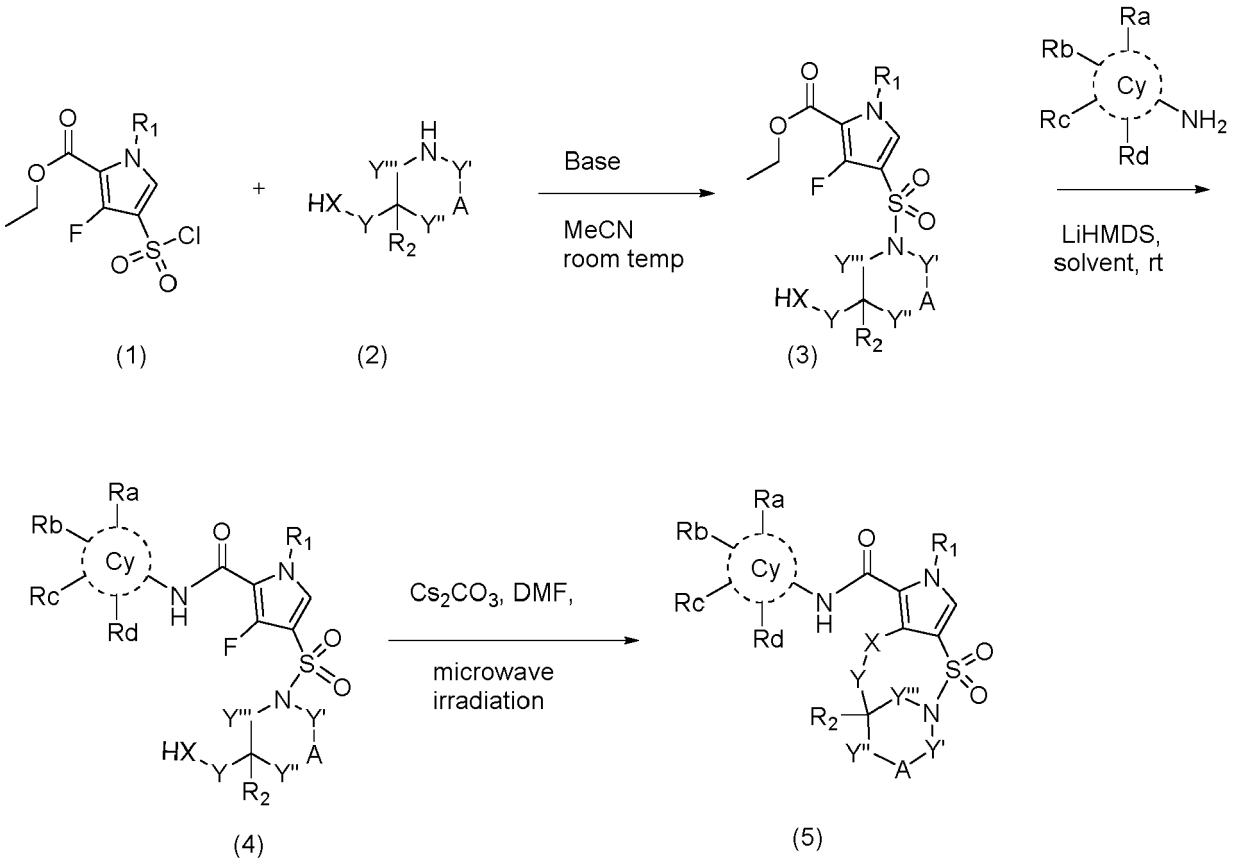
Method 1: column 1, run time: 3 minutes, run gradient: 5%B to 100%B in 2.80 min + 100%B for 0.2 min, equilibration time: 0,8 min, ionization mode: ESI+.
Method 2: column 2, run time: 4 minutes, run gradient: 0%B to 45%B in 3.5 min + 45%B to 100%B in 0.05 min +100%B for 0.45 min, equilibration time: 0,8 min, ionization mode: ESI$^+$.
Method 3: column 3, run time: 6 minutes, run gradient: 5%B to 100%B in 5 min + 100%B for 1 min, equilibration time: 2 min.
Method 4: column 3, run time: 6 minutes, run gradient: 5%B to 50%B in 5 min + 50%B to 100%B in 0.2 min 100%B for 0.8 min, equilibration time: 2 min, ionization mode: ESI$^+$.
Method 5: column 1, run time: 3 minutes, run gradient: 5%B to 100%B in 2.80 min + 100%B for 0.2 min, equilibration time: 0,8 min, ionization mode: ESI+.
Method 6: column 2, run time: 4 minutes. run gradient: 0%B to 45%B in 3.5 min + 45%B to 100%B in 0.05 min +100%B for 0.45 min. Equilibration time: 0,8 min, ionization mode: ESI$^+$.
Method 7: column 3, run time: 6 minutes, run gradient: 5%B to 100%B in 5 min + 100%B for 1 min, equilibration time: 2 min, ionization mode: ESI$^+$.
Method 8: column 3, run time: 6 minutes, run gradient: 5%B to 50%B in 5 min + 50%B to 100%B in 0.2 min 100%B for 0.8 min, Equilibration time: 2 min, ionization mode: ESI$^+$.
Method 9: column 1. run time: 4 minutes, column 1, run time: 4 minutes, run gradient:5%B to 100%B in 3.00 min + 100%B for 1 min, equilibration time: 0,8 min, ionization mode: ESI$^+$.
Method 10: column 1. run time: 4 minutes, run gradient: 5%B to 100%B in 3.00 min + 100%B for 1 min, equilibration time: 0,8 min, Ionization Mode: ESI$^-$.

Method 11: column 1, run time: 3 minutes, run gradient: 40%B to 100%B in 2.80 min + 100%B for 0.2 min, equilibration time: 0,8 min. Ionization Mode: ESI^+.
Method 12: column 3, run time: 6 minutes, run gradient: 25%B to 70%B in 5 min + 100%B for 1 min, equilibration time: 2 min, Flow: 0,5 mL/min, ionization mode: ESI^+.

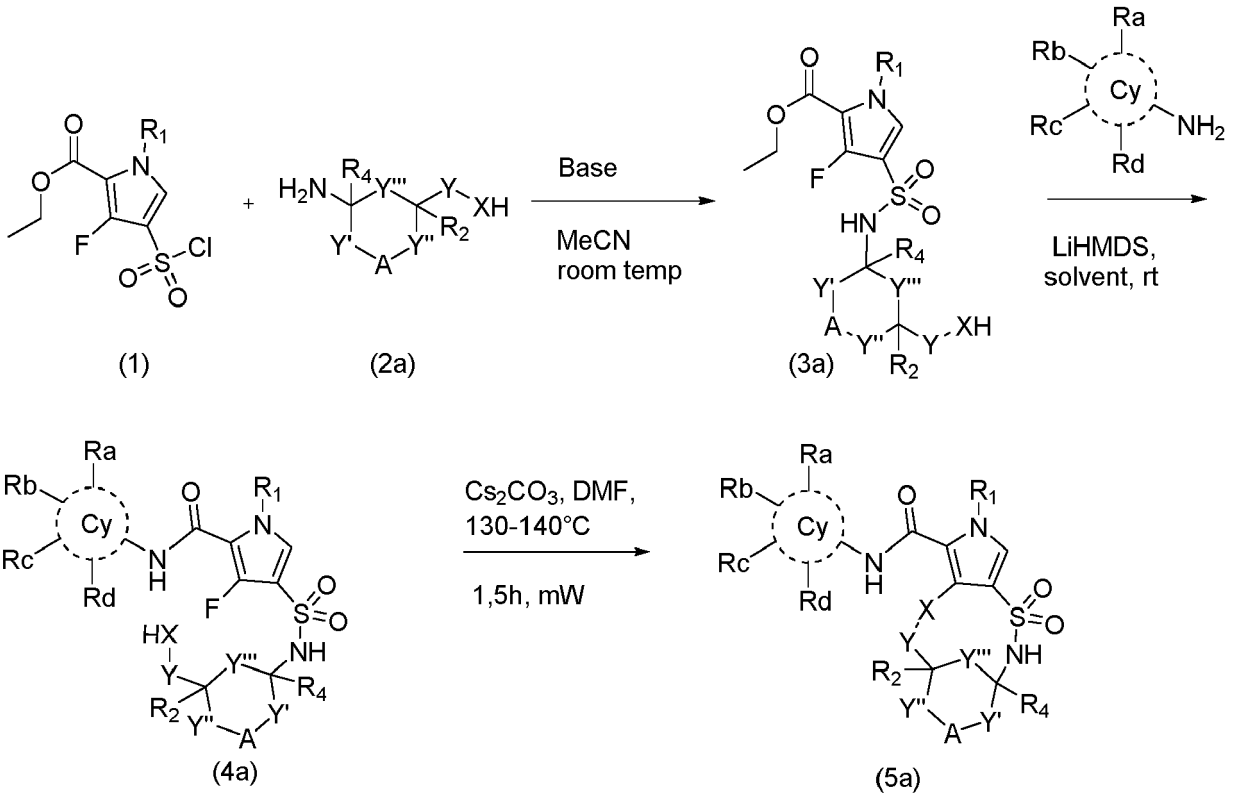
Synthesis

[0133] According to a further aspect of the invention there is provided a process for the preparation of compounds of formula (I), (Ia) or (Ib) or salts thereof. The following schemes are examples of synthetic schemes that may be used to synthesise the compounds of the invention. In the following schemes reactive groups can be protected with protecting groups and deprotected according to well established techniques. In the following schemes unless otherwise indicated R_1, R_2, R_4, A, X, Y, Y', Y", Y"', Cy, Ra, Rb, Rc, Rd are as defined herein above in formula (I), (Ia) or (Ib).

[0134] It will be understood by those skilled in the art that certain compounds of the invention can be converted into other compounds of the invention according to standard chemical methods. Compounds of the invention may be prepared according to the general routes indicated in the following Scheme 1 and Scheme 2:

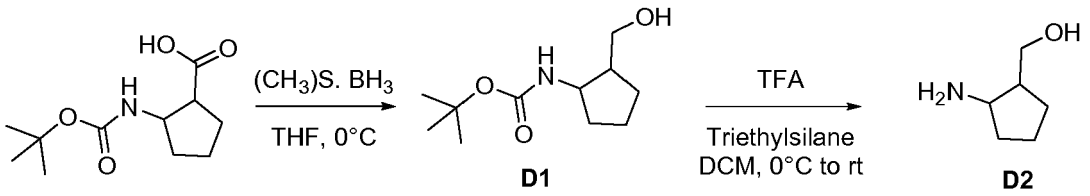


Scheme 1

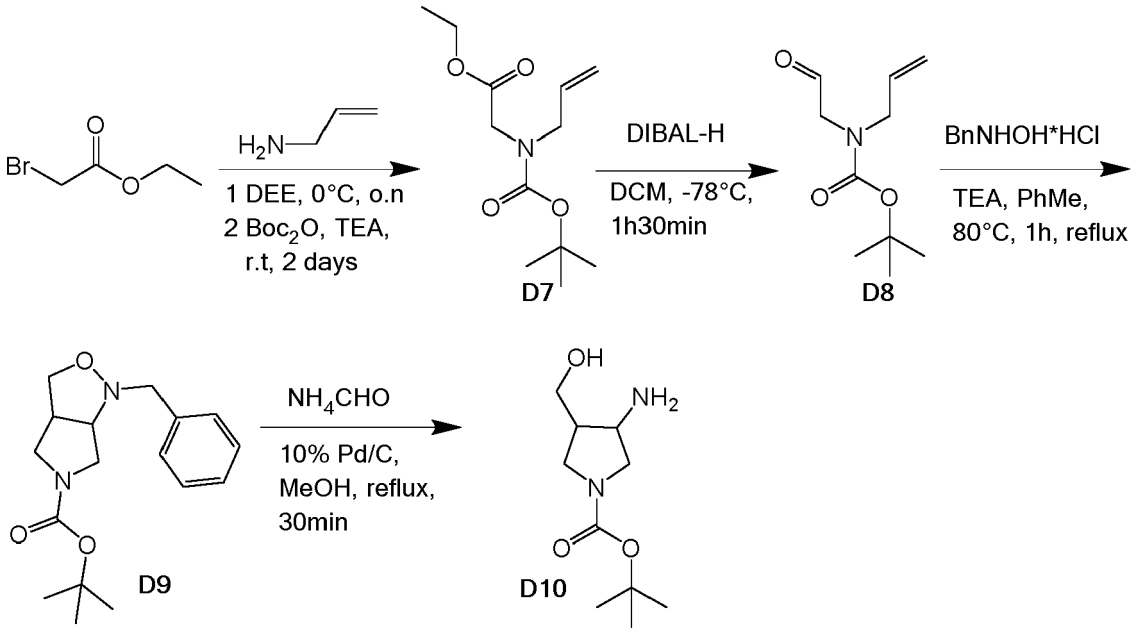


Scheme 2

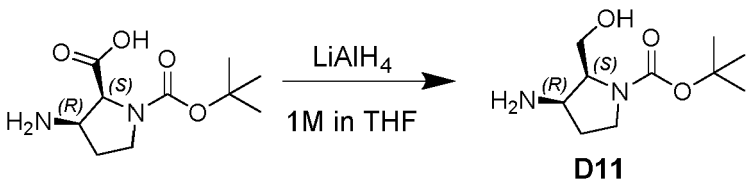
[0135] Ethyl 4-(chlorosulfonyl)-3-fluoro-1-methyl-1H-pyrrole-2-carboxylate, indicated as compound (1) in Scheme 1 and Scheme 2, was prepared according to the procedure described in WO2017/001655. According to Scheme 1, a cyclic amine derivative bearing a nucleophilic -XH substituent is reacted with the compound (1) in the presence of the appropriate base to give the corresponding sulphonamide product (3). Reaction of (3) with an arylamine in the presence of a strong non-nucleophilic base such as lithium bis(trimethylsilyl)amide LiHMDS in a solvent like tethrahydrofuran, converts the ethyl carboxylate into an arylamide derivative (4). A subsequent cyclization step through intramolecular nucleophilic attack of the XH on the fluorine gives the tricyclic core of compound (5). The synthetic pathway outlined in Scheme 2 is very similar to the one in Scheme (1), but uses a primary amine of structure (2a). Depending on the specific nature of A in compounds (5) or (5a), the product can be further elaborated through protection, deprotection or further functionalization steps. In particular, when A is a nitrogen derivative it can be protected as the N-Boc derivative. The Boc can be removed by acidic treatment and the resulting NH can be further converted for example into a carbamate, urea, sulphonamide, sulphonyl urea derivative or can be alkylated through, for example, reductive amination chemistry. Certain amine derivatives (2) of Scheme 1 and (2a) of Scheme 2 were prepared according to the synthetic strategies outlined in Schemes 3, 4 and 5. The procedures in the schemes can be used for the synthesis of the compounds indicated below and can be used as well for the synthesis of the compounds as single diastereoisomers and/or enantiomers by choosing the appropriate starting materials. In particular, Scheme 3 refers to the synthesis of D2 and applies also to the syntheses of **D4** and **D6.**



Scheme 3



Scheme 4



Scheme 5

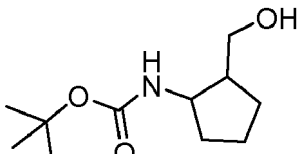
[0136] Where not otherwise indicated, starting materials and/or intermediates were obtained from commercial sources or can be obtained through synthetic procedures known in the chemistry literature. The indication of the commercial source of certain compounds in the description of the experimental procedure, when provided, is only for easy reference to skilled chemist and should not be interpreted as the indication to use only that particular commercial compound.

[0137] In the following paragraphs, the Descriptions 1 to 46 illustrate the preparation of intermediates used to make compounds of formula (I), (Ia) or (Ib) and salts thereof. The Examples illustrates the preparation of the compounds of the invention and salts thereof. Where the compounds have more than one chiral center, it is understood that they might exist as mixtures of diastereoisomers or as single isomers. Both racemic and chiral compounds are within the scope of the present invention. The indicated procedures are provided merely for assistance to the skilled chemist. The starting material may not necessarily have been prepared from the batch of the Description or the Example referred to.

Examples

Description 1: tert-butyl cis-(2-(hydroxymethyl)cyclopentyl)carbamate (D1)

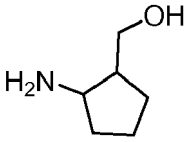
[0138]



[0139] To a solution of cis-2-Boc-amino-cyclopentanecarboxylic acid (200 mg, 0,87 mmol) in dry THF (4 mL), borane dimethylsulfide complex (0.4 mL, 4.33 mmol) was added at 0°C. After 10 min mixture was allowed to warm at room temperature. After 1h a further aliquot of borane dimethylsulfide (0.4 mL, 4.33 mmol) was added and after 2.5h conversion was completed. Mixture was quenched by slow addition of methanol at 0°C, and then solvent was removed under reduced pressure to afford **D1** as a white solid (195 mg, y>100%) that was used without purification. Method 1: Rt=1.54 min, m/z=216 $(M+H)^+$.

Description 2: *cis*-(2-aminocyclopentyl)methanol (D2)

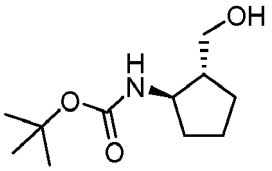
[0140]



[0141] To a stirred solution of **D1** (195 mg, 0.9mmol) in DCM (5 mL), trifluoroacetic acid (0.350 mL, 4.6 mmol) and triethylsilane (0.160 ml,) were added at 0°C. After 5 min, the reaction mixture was allowed to warm at room temperature. After 2h additional aliquots of trifluoroacetic acid (0.150 mL, 1.96 mmol) and triethylsilane (0.080 mL) were added. Reaction went to completion after 2.5h and mixture evaporated under reduced pressure to afford **D2** trifluoracetate as a white solid (429 mg, y>100%) that was used in next step without purification, m/z = 116 $(M+H)^+$.

Description 3: tert-butyl ((1R,2R)-2-(hydroxymethyl)cyclopentyl)carbamate (D3)

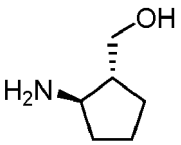
[0142]



[0143] To a stirred solution of (1R,2R)-2-((tert-Butoxycarbonyl)amino)cyclopentanecarboxylic acid (113 mg, 0.49 mmol) in THF (2 mL), borane dimethylsulfide complex 2M in THF (1.2 mL, 2.4 mmol) was added at 0°C. After 5 min mixture was allowed to warm at rt. After 1 h mixture was quenched with slow addition of MeOH at 0°C, diluted with DCM and washed with HCl 1N and water. Organic layer was dried over Na_2SO_4, filtered and solvent removed under reduced pressure to afford **D3** as a white solid (101 mg). Method 1: Rt=1.50 min, m/z=216 $(M+H)^+$.

Description 4: ((1R,2R)-2-aminocyclopentyl)methanol (D4)

[0144]

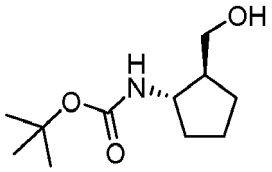


[0145] To a stirred solution of **D3** (101 mg, 0.469 mmol) in DCM (3 mL), trifluoroacetic acid (0.180 mL, 2.3457 mmol) and triethylsilane (0.085 mL, 0.532 mmol) were added at 0°C. After 5 min the reaction mixture was allowed to warm up

to room temperature. After 3.5h the reaction mixture was quenched with NaOH 5M (1.5 mL) and stirred for 5 minutes. Mixture was evaporated under reduced pressure, then suspended in acetonitrile and filtered over Na_2SO_4 pad to remove part of salts and water to afford **D4** as a white sticky solid (746 mg) that was used in the next step without purification. Method 1: Rt=0.36 min, m/z=116 $(M+H)^+$.

Description 5: *tert*-butyl ((1S,2S)-2-(hydroxymethyl)cyclopentyl)carbamate (D5)

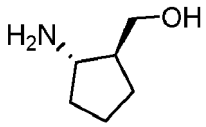
[0146]



[0147] Prepared similarly as described for compound **D3** starting from (1S,2S)-2-((tert-butoxycarbonyl)amino)cyclopentanecarboxylic to give **D5.** Method 1: Rt=1.50 min, m/z=216 $(M+H)^+$.

Description 6: ((1S,2S)-2-aminocyclopentyl)methanol (D6)

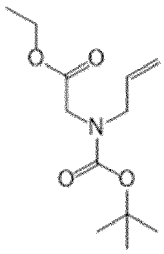
[0148]



[0149] Prepared from **D5,** following same procedure as described for compound **D4.** Method 1: Rt=0.36 min, m/z=116 $(M+H)^+$.

Description 7: Ethyl N-allyl-N-(tert-butoxycarbonyl)glycinate (D7)

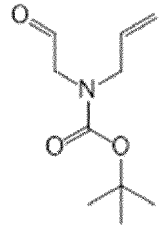
[0150]



[0151] The compound was prepared according to US2006148722. A solution of prop-2-en-1-amine (2.92mL, 38.92mmol) in diethylether (17mL) was cooled at 0°C in a dry ice/acetone bath in a sealed 20mL vial. Ethyl 2-bromoacetate (3.74mL, 19.46mmol) was added in 200-300uL portions over 10min. A white precipitate was formed. After one night at room temperature, the mixture was filtered and the filtrate was evaporated at reduced pressure (200mmbar). The residue (6g) was dissolved in DCM (200mL), treated with triethylamine (2.7mL, 19.46mmol) and cooled to 0°C with ice bath. The resulting solution was treated with di-tert-butyl dicarbonate (4.25g, 19.46mmol) and stirred for 2 days at room temperature. Solvent was removed under reduced pressure and partitioned between water and EtOAc. The organic layer was washed with brine (X2) and 5% citric acid acq. solution, dried over Na_2SO_4 (anh.), filtered and evaporated. The residue (yellowish mobile oil) was purified by flash chromatography (direct phase, eluent 95/5 PE/DCM), giving about 5g of N-allyl-N-(tert-butoxycarbonyl)glycinate (**D7**) as colourless oil. ^1H NMR (300 MHz, $CDCl_3$) δ ppm 1.04 - 1.29 (m, 3 H) 1.29 - 1.50 (m, 9 H) 3.54 - 3.99 (m, 4 H) 4.12 (q, J=7.09 Hz, 2 H) 4.92 - 5.19 (m, 2 H) 5.45 - 6.01 (m, 1H); Method 1, Rt= 2.06min. m/z=143.07 $(M+H)^+$.

Description 8: tert-butyl allyl(2-oxoethyl)carbamate (D8)

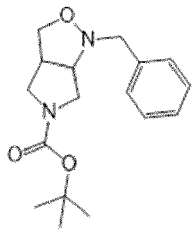
[0152]



[0153] The compound was prepared according to procedure described in WO2010/016005. A solution of **D7** ethyl N-allyl-N-(tert-butoxycarbonyl)glycinate (1g, 4.11mmol) in DCM (11mL) was cooled to -78°C with acetone/ dry ice bath under nitrogen atmosphere. 1M DIBAL-H in DCM (8.22mL, 8.22mmol) was added over 1hr with a syringe pump. The reaction mixture was stirred at -78°C for 30min. The reaction was stopped by addition of NH_4Cl sat. solution (1.2mL) and 2N HCl (4mL) in a single portion, then the reaction was magnetically stirred giving a white mixture. The reaction mixture was partitioned between water and DCM, treated with potassium sodium tartrate tetrahydrate (Rochelle's salt) until saturation, magnetically stirred for 15min then further extracted with DCM. The combined organic extracts were dried over $MgSO_4$ (anh.), filtered and finally evaporated giving **D8** tert-butyl allyl(2-oxoethyl)carbamate (0.8g, 4.015mmol) as a white sticky oil. Method 1, Rt= 1.58min. m/z=200 $(M+H)^+$.

Description 9: cis-tert-butyl 1-benzyltetrahydro-1H-pyrrolo[3,4-c]isoxazole-5(3H)-carboxylate (D9)

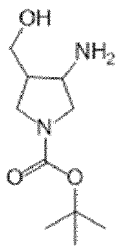
[0154]



tert-Butyl-allyl-(2-oxoethyl)carbamate (0.8g, 4.02mmol) **D8** and N-benzylhydroxylamine (0.99g, 8.03mmol) were suspended in toluene (32mL) and triethylamine (0.61mL, 4.42mmol). The mixture was heated at 80°C for about 1hr and at room temperature overnight. The reaction was poured into a separating funnel, diluted with EtOAc, washed with $NaHCO_3$ (sat. solution), 5% citric acid acq. solution and brine then evaporated. The crude residue (1g) was purified by flash chromatography over silica gel (eluent: EtOAc/PE) to obtain **D9** cis-tert-butyl 1-benzyltetrahydro-1H-pyrrolo[3,4-c]isoxazole-5(3H)-carboxylate (0.6g, 1.97mmol) as a colorless oil. Method 1, Rt= 1.94min. m/z=305.29 $(M+H)^+$.

Description 10: tert-butyl cis-3-amino-4-(hydroxymethyl)pyrrolidine-1-carboxylate (D10)

[0155]

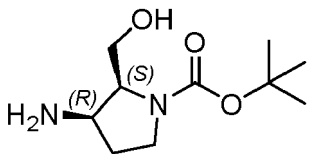


[0156] A solution of **D9** cis-tert-butyl 1-benzyltetrahydro-1H-pyrrolo[3,4-c]isoxazole-5(3H)-carboxylate (0.55g, 1.81mmol) in methanol (30mL) was treated with a single portion of ammonium formate (0.57mg, 9.03mmol) and 10%

Pd/C (50mg). The mixture was refluxed for 30min, then cooled to room temperature and filtered on celite, washing with methanol. Solvent was removed in vacuo, affording **D10** tert-butyl cis-3-amino-4-(hydroxymethyl)pyrrolidine-1-carboxylate (0.4g,1.85mmol) as colourless oil. Method 1, Rt= 0.86min. m/z=217.26 $(M+H)^+$. ^1H NMR (300 MHz, DMSO-d6+TFA) δ ppm 1.51 (s, 9 H) 2.65 - 2.73 (m, 1 H) 3.19 - 3.39 (m, 1 H) 3.43 - 3.79 (m, 5 H) 3.82 - 4.01 (m, 1 H) 8.03 (br s, 3 H).

Description 11: *tert*-butyl (2S,3R)-3-amino-2-(hydroxymethyl)pyrrolidine-1-carboxylate (D11)

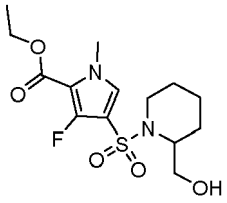
[0157]



[0158] 2-Methyl 1-(2-methyl-2-propanyl) (2S,3R)-3-amino-1,2-pyrrolidinedicarboxylate hydrochloride (Fluorochem, cat n° 515165) (1:1) (200mg, 0.712mmol, leq) was suspended in dry THF (5.5mL), the mixture was cooled to 0°C, 1M solution of lithium aluminium hydride in THF (3mL, 3mmol, 4.2eq) was added in 10min and then reaction mixture was stirred at the same temperature. Reaction was quenched after 1h. Satured Rochelle salt solution (1.5mL) was added to reaction mixture at 0°C, it was allowed to warm up to rt, it was filtered to remove salts. Then, DCM was added, organic layer was washed once with brine, dried over sodium sulfate, filtered and solvent was removed under reduced pressure affording **D11** a colourless oil (134mg). Method 4: Rt=1.14 min, MH+ = 217 m/z $(M+H)^+$. Stereochemistry cis, single enantiomer.

Description 12: Ethyl 3-fluoro-4-((2-(hydroxymethyl)piperidin-1-yl)sulfonyl)-1-methyl-1H-pyrrole-2-carboxylate (D12)

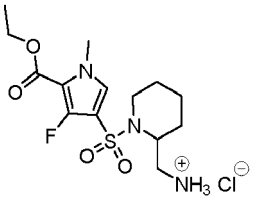
[0159]



[0160] DIPEA (0.1mL, 0.56 mmol) and piperidin-2-ylmethanol (32.03mg, 0.28mmol) were added to a stirred solution of ethyl 4-(chlorosulfonyl)-3-fluoro-1-methyl-1H-pyrrole-2-carboxylate (50mg,0.190mmol) in MeCN (1.8mL,0.035mol) and stirring was continued for 1h at room temperature. Volatiles were evaporated and the residue was partitioned between sat. NH_4Cl solution and EtOAc. The organic layer was separated, dried over Na_2SO_4, evaporated under reduced pressure and purified by flash chromatography on silica gel (Petroleum ether/ EtOAc) to obtain the title compound **D12** (41.62mg). m/z=349 $(M+H)^+$.

Description 13: (1-((5-(ethoxycarbonyl)-4-fluoro-1-methyl-1H-pyrrol-3-yl)sulfonyl)piperidin-2-yl)methanaminium chloride (D13)

[0161]

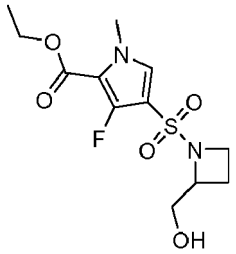


[0162] DIPEA (0.1mL, 0.560mmol) and tert-butyl (piperidin-2-ylmethyl)carbamate (59.6mg, 0.28mmol) were added to

to a stirred solution of ethyl 4-(chlorosulfonyl)-3-fluoro-1-methyl-1H-pyrrole-2-carboxylate (50mg, 0.190mmol) in MeCN (1.84mL, 0.035mol) and stirring was continued overnight at room temperature. Volatiles were evaporated and the residue was partitioned between sat. NH_4Cl solution and EtOAc. The organic layer was separated, dried over Na_2SO_4, evaporated under reduced pressure and purified by flash cromatography on silica gel (Petroleum ether/EtOAc) to give ethyl 4-((2-(((tert-butoxycarbonyl)amino)methyl)piperidin-1-yl)sulfonyl)-3-fluoro-1-methyl-1H-pyrrole-2-carboxylate (77.82mg, y= 93.8%). Method 1: Rt=2.15min. m/z=348.18 $(M-100)^+$ Exact mass=447.18. The Boc protecting group was removed by dissolving the intermediate ethyl 4-((2-(((tert-butoxycarbonyl)amino)methyl)piperidin-1-yl)sulfonyl)-3-fluoro-1-methyl-1H-pyrrole-2-carboxylate in dioxane (1.7mL) and treating with hydrogen chloride 4N in dioxane (2.81mL,11.25mmol) at RT for 1h. Volatiles were evaporated under reduced pressure to afford **D13** as HCl salt, in about quantitative yield (66.75mg). Method 1: Rt= 1.18min. m/z=348.13 $(M+H)^+$ Exact mass=347.18.

Description 14: Ethyl 3-fluoro-4-((2-(hydroxymethyl)azetidin-1-yl)sulfonyl)-1-methyl-1H-pyrrole-2-carboxylate (D14)

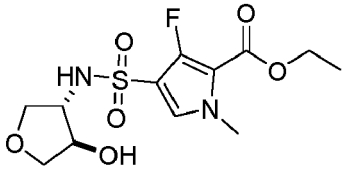
[0163]



[0164] Methyl 2-azetidinecarboxylate hydrochloride (89.44mg, 0.590mmol) in THF (11.9mL, 0.147mol) was added to lithium aluminium hydride (1.48mL,1.48mmol) 1M cooled to 0°C. The reaction mixture was stirred at 0°C for 2 h. After quenching with water (5.0 equiv) the mixture was concentrated in vacuo to obtain azetidin-2-ylmethanol. DIPEA (0.16mL,0.930mmol) and azetidin-2-ylmethanol (24.2mg,0.280mmol) were added to a stirred solution of ethyl 4-(chlorosulfonyl)-3-fluoro-1-methyl-1H-pyrrole-2-carboxylate (50mg,0.190mmol) in MeCN (1.8mL,0.035mol) and stirring was continued for 2h. Volatiles were evaporated and the residue was partitioned between saturated NH_4Cl solution and EtOAc. The organic layer was separated, dried over Na_2SO_4, evaporated under reduced pressure and purified by flash cromatography on silica gel (Petroleum ether/ EtOAc) to obtain approximately 11 mg of the title compound **D14.** Method 1: Rt= 1.44min. m/z=320,97 $(M+H)^+$.

Description 15: trans ethyl 3-fluoro-4-(N-(4-hydroxytetrahydrofuran-3-yl)sulfamoyl)-1-methyl-1H-pyrrole-2-carboxylate (D15)

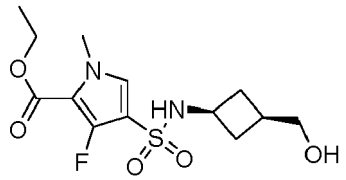
[0165]



[0166] DIPEA (0.23mL, 1.330mmol) and trans-4-aminotetrahydrofuran-3-ol (68.8mg,0.670mmol) were added to a stirred solution of ethyl 4-(chlorosulfonyl)-3-fluoro-1-methyl-1H-pyrrole-2-carboxylate (120mg, 0.440mmol) in MeCN (4.4mL) and stirring was continued for 1h at room temperature. Volatiles were evaporated and the residue was partitioned between saturated NH_4Cl solution and EtOAc. The organic layer was separated, dried over Na_2SO_4, evaporated under reduced pressure and purified by flash cromatography on silica gel (Petroleum ether/EtOAc) to obtain the title compound **D15** as a trans 3S,4R and 3R,4S racemate (133mg, y= 88.9%). Method 1: Rt= 1.25min. m/z=337 $(M+H)^+$.

Description 16: *cis*-Ethyl 3-fluoro-4-(N-((3-(hydroxymethyl)cyclobutyl)sulfamoyl)-1-methyl-1H-pyrrole-2-carboxylate (D16)

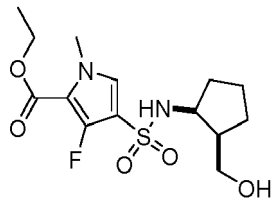
[0167]



[0168] To a solution of tert-butyl (cis-3-(hydroxymethyl)cyclobutyl)carbamate (0.154 g, 0.765 mmol) in DCM (2 mL), HCl 4N in dioxane (0.4 mL, 1.6 mmol) was added at rt. After 5h30 min a further aliquot of HCl 4N in dioxane (0.8 mL, 3.2 mmol) was added and mixture was left at rt until complete conversion. Mixture was evaporated under reduced pressure to obtain *cis*-3-(hydroxymethyl)cyclobutan-1-aminium chloride as a white solid (128 mg). Method 1: Rt=0.83 min, m/z=102 $(M+H)^+$. The crude compound (38.5 mg, 0.280 mmol) was taken in dry acetonitrile (1.7 mL) and dry DIPEA (0.1 mL, 0.574 mmol) and ethyl 4-(chlorosulfonyl)-3-fluoro-1-methyl-1H-pyrrole-2-carboxylate (50 mg, 0.185 mmol) were added at room temperature. Reaction mixture was stirred overnight and then evaporated under reduced pressure to afford a light brown solid. Crude was purified with flash chromatography (Petroleum ether/AcOEt) to afford **D16** as a white solid (45 mg). m/z = 335 $(M+H)^+$.

Description 17: cis-Ethyl 3-fluoro-4-(N-(2-(hydroxymethyl)cyclopentyl)sulfamoyl)-1-methyl-1H-pyrrole-2-carboxylate (D17)

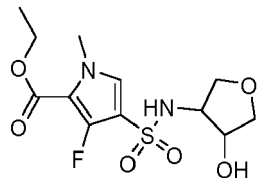
[0169]



[0170] To a solution of **D2** (176 mg, 0.371 theoretical mmol) and ethyl 4-(chlorosulfonyl)-3-fluoro-1-methyl-1H-pyrrole-2-carboxylate (50 mg, 0.185 mmol) in dry acetonitrile (1.7 mL), dry DIPEA (0.130 mL, 0.746 mmol) was added at room temperature. After 3h a further aliquot of **D2** (102 mg, 0.214 theoretical mmol) was added. Reaction was stopped after 6h, crude was purified with preparative HPLC-MS (H_2O/CH_3CN+0.1% TFA) to give **D17** as a white powder (18 mg, y= 28%). The compound is the cis racemate at the cyclopentyl ring (SR and RS). Method 1: Rt=1.62 min, m/z=349 $(M+H)^+$.

Description 18: trans-Ethyl 3-fluoro-4-(N-(4-(hydroxymethyl)tetrahydrofuran-3-yl)sulfamoyl)-1-methyl-1H-pyrrole-2-carboxylate (D18)

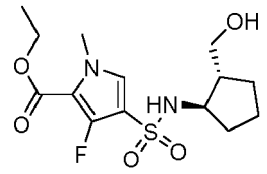
[0171]



[0172] To a solution of 4-aminotetrahydrofuran-3-ol (74.5 mg, 0.722 mmol) and ethyl 4-(chlorosulfonyl)-3-fluoro-1-methyl-1H-pyrrole-2-carboxylate (150 mg, 0.556 mmol) in dry acetonitrile (4 mL), dry DIPEA (0.3 mL, 1.7223 mmol) was added at rt. After 1h mixture was evaporated under reduced pressure to afford a yellow solid (325 mg). Crude was purified by flash chromatography (Petroleum ether/AcOEt) to afford **D18** as a light yellow solid (178 mg, y= 95%). Method 1: Rt=1.28 min, m/z=337 $(M+H)^+$. The compound is the trans racemic mixture at the tetrahydrofuranyl ring.

Description 19: Ethyl 3-fluoro-4-(N-((IR,2R)-2-(hydroxymethyl)cyclopentyl)sulfamoyl)-1-methyl-1H-pyrrole-2-carboxylate (D19)

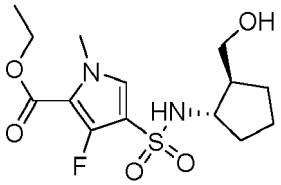
[0173]



[0174] To a solution of **D4** (373 mg, 0.234 theoretical mmol) in dry acetonitrile (1.5 mL), ethyl 4-(chlorosulfonyl)-3-fluoro-1-methyl-1H-pyrrole-2-carboxylate (50 mg, 0.185 mmol) and dry DIPEA (0.1 mL, 0.574 mmol) were added at rt. After 1.5h more **D4** (124.3 mg, 0.191 mmol) in dry acetonitrile (0.5 mL) was added. Conversion was completed; mixture was diluted with DCM and washed with water (x2). Organic layer was dried over Na_2SO_4, filtered and then evaporated under reduced pressure. Crude was purified with flash chromatography (ETP/AcOEt to afford **D19** as a yellow solid (59 mg). Method 1: Rt=1.60 min, m/z=349 $(M+H)^+$.

Description 20: Ethyl 3-fluoro-4-(N-((1S,2S)-2-(hydroxymethyl)cyclopentyl)sulfamoyl)-1-methyl-1H-pyrrole-2-carboxylate (D20)

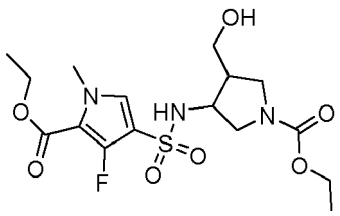
[0175]



[0176] The compound was prepared from **D6,** following the same procedure indicated for compound **D19.** Method 1: Rt=1.60 min, m/z=349 $(M+H)^+$.

Description 21: cis-ethyl 4-(N-(1-(ethoxycarbonyl)-4-(hydroxymethyl)pyrrolidin-3-yl)sulfamoyl)-3-fluoro-1-methyl-1H-pyrrole-2-carboxylate (D21)

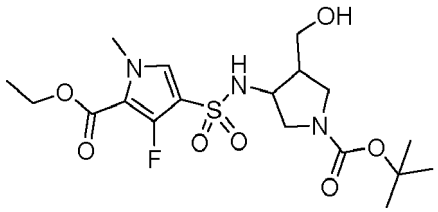
[0177]



[0178] To a suspension of ethyl 4-(chlorosulfonyl)-3-fluoro-1-methyl-1H-pyrrole-2-carboxylate (70mg, 0.260 mmol) and ethyl 3-amino-4-(hydroxymethyl)-1-pyrrolidinecarboxylate (56.2 mg, 0.299 mmol) in dry acetonitrile (2 mL), dry DIPEA (0.1 mL, 0.574 mmol) was added at room temperature. After 1.5h mixture was diluted with DCM and washed with 5% citric acid solution. Organic layer was dried over Na_2SO_4, filtered and solvent removed under reduced pressure to afford **D21** as a light yellow solid (162 mg). The compound is the cis racemate at the pyrrolidine ring (racemate of 3S,4S and 3R,4R). Crude was purified by flash chromatography (Petroleum ether/AcOEt) to afford a white solid (101 mg). Method 1: Rt=1.52 min, m/z=422 $(M+H)^+$.

Description 22: cis-ethyl 4-(N-(1-(tert-butoxycarbonyl)-4-(hydroxymethyl)pyrrolidin-3-yl)sulfamoyl)-3-fluoro-1-methyl-1H-pyrrole-2-carboxylate (D22)

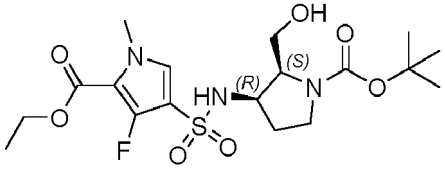
[0179]



[0180] To a suspension of ethyl 4-(chlorosulfonyl)-3-fluoro-1-methyl-1H-pyrrole-2-carboxylate (449mg, 1.66mmol) and **D10** (360mg, 1.66mmol) in dry MeCN (9 mL), DIPEA (0.72mL, 4.16mmol) was added dropwise at RT. Reaction mixture was stirred at RT for 2h (a off-white solid precipitated). Solid was filtered and washed with a small amount of cold acetonitrile, to obtain **D22** as off-white powder (570mg). The compound is the cis racemate at the pyrrolidine ring (racemate of 3S,4S and 3R,4R). ^{1}H NMR (300 MHz, DMSO-d_6+TFA) δ ppm 1.28 (t, J=6.97 Hz, 3 H) 1.37 (d, J=8.99 Hz, 9 H) 2.26 - 2.36 (m, 1 H) 3.04 - 3.14 (m, 1 H) 3.16 - 3.42 (m, 4 H) 3.46 - 3.57 (m, 1 H) 3.75 - 3.89 (m, 4 H) 4.27 (q, J=6.79 Hz, 2 H) 7.56 (d, J=4.77 Hz, 1 H) 7.82 - 8.06 (m, 1 H). Method 1: Rt=1.74min. m/z=450.40 $(M+H)^+$.

Description 23: Ethyl 4-(N-((2S,3R)-1-(tert-butoxycarbonyl)-2-(hydroxymethyl)pyrrolidin-3-yl)sulfamoyl)-3-fluoro-1-methyl-1H-pyrrole-2-carboxylate (D23)

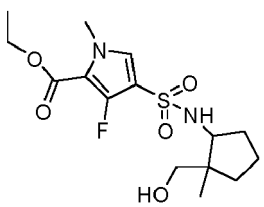
[0181]



[0182] Crude **D11**, 100mg, 0.462mmol, leq) and ethyl 4-(chlorosulfonyl)-3-fluoro-1-methyl-1H-pyrrole-2-carboxylate (125mg, 0.464mmol, leq) were dissolved in dry acetonitrile (4mL), N,N-diisopropylethylamine (165uL, 0.925mmol, 2eq) was added dropwise and reaction mixture was stirred at rt. Complete conversion after 15min. Reaction mixture was diluted with ethyl acetate, organic layer was washed once with satured ammonium chloride aqueous solution and once with brine. Organic layer was dried over sodium sulfate, filtered and solvent was removed under reduced pressure affording an orange solid (256mg). Crude product was purified by flash chromatography (DCM/EtOAc 70/30) to afford **D23** as a white solid (181mg). Method 1: Rt=1.85 min, MH+ = 450 m/z. Stereochemistry cis, single enantiomer.

Description 24: ethyl 3-fluoro-4-(N-(2-(hydroxymethyl)-2-methylcyclopentyl)sulfamoyl)-1-methyl-1H-pyrrole-2-carboxylate (D24)

[0183]

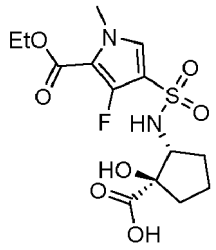


[0184] (2-amino-1-methylcyclopentyl)methanol (58 mg, 0.449 mmol, 1.1 eq) was suspended in dry MeCN (2.5 mL) under a nitrogen atmosphere, ethyl 4-(chlorosulfonyl)-3-fluoro-1-methyl-1H-pyrrole-2-carboxylate (110 mg, 0.408 mmol) was added, followed by dry DIPEA (156 uL, 0.897 mmol, 2.2 eq) and the reaction was stirred at rt for 1h: complete conversion. The reaction was diluted with DCM and washed with 5% citric acid (2x); the organic phase was washed

with brine, dried over Na_2SO_4 and evaporated, yielding 128mg of **D24** as a pale yellow powder, used without further purification. Method 1: Rt=1.70 min; m/z 363 $(M+H)^+$.

Description 25: cis-2-[(5-ethoxycarbonyl-4-fluoro-1-methyl-1H-pyrrole)-3-sulfonamido]-1-hydroxycyclopentane-1-carboxylic acid (D25)

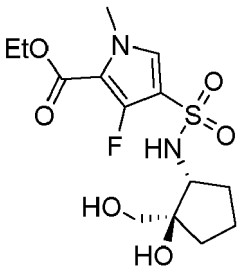
[0185]



[0186] (1R2R and 1S2S) cis-methyl-2-amino-1-hydroxycyclopentane-1-carboxylate, oxalate salt (72mg, 0.29mmol) was suspended in EtOH (2.8mL); 2N NaOH (0.433mL, 0.867mmol, 3eq) was added and the mixture was stirred at rt for 24h. The mixture was brought to acidic pH with 2N HCl (0.5mL) and the volatiles were evaporated, obtaining 128 mg of crude cis 2-amino-1-hydroxycyclopentane-1-carboxylic acid hydrochloride, used as such. Method 2: Rt = 0.59 min, MH+ = 146. The crude (racemate of *1R2R* and 1*S2S)* cis-2-amino-1-hydroxycyclopentane-1-carboxylic acid hydrochloride (0.289 mmol, leq) was suspended in dry MeCN (2.5 mL) under a nitrogen atmosphere; ethyl 4-(chlorosulfonyl)-3-fluoro-1-methyl-1H-pyrrole-2-carboxylate (85.7 mg, 0.318 mmol, 1.1eq) was added, followed by dry DIPEA (262 uL, 1.5 mmol, 5.2 eq) and the reaction was stirred at rt for 2h. The reaction was diluted with DCM and washed with 5% citric acid; the organic phase was dried over Na_2SO_4 and evaporated, yielding 95 mg of crude product. 35mg of **D25** were obtained after purification by preparative HPLC (H_2O, CH_3CN 0.1% HCOOH). Method 1: Rt=1.42 min; m/z 379 $(M+H)^+$.

Description 26: (*1R2R, 1S2S*)cis-ethyl 3-fluoranyl-4-[[2-(hydroxymethyl)-2-oxidanyl-cyclopentyl]sulfamoyl]-1-methyl-pyrrole-2-carboxylate (D26)

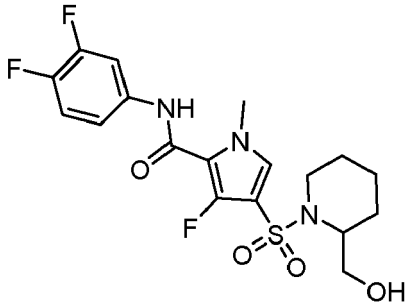
[0187]



[0188] **D25** (35mg, 0.093mmol) was dissolved in dry THF (1.5mL) under a nitrogen atmosphere. The solution was cooled in an ice bath and more aliquots of 2M $(CH_3)_2S.BH_3$ in THF (0.1mL, 0.2mmol, 2.16eq) were added dropwise. The reaction was stirred at rt for 16h and stopped when approximately 10% of the starting acid was still unreacted. The reaction was cooled in ice and MeOH (0.4mL) was added up to end of foaming. The reaction was stored at -20°C for 16h, then it was diluted with DCM and washed with a saturated solution of $NaHCO_3$. The organic phase was dried over Na_2SO_4 and evaporated, yielding 21mg of crude **D26** as a colourless thick oil, used without further purification. Method 1: Rt=1.38 min; m/z 365 $(M+H)^+$.

Description 27: N-(3,4-difluorophenyl)-3-fluoro-4-((2-(hydroxymethyl)piperidin-1-yl)sulfonyl)-1-methyl-1H-pyrrole-2-carboxamide (D27)

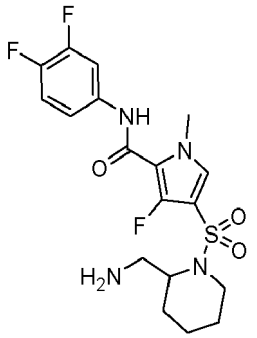
[0189]



[0190] To a suspension of **D12** (41.3mg, 0.12mmol) and 3,4-difluoroaniline (0.014mL, 0.14mmol) in dry THF (0.75mL), lithium bis(trimethylsilyl)amide 1M in THF (0.66mL, 0.66mmol) was added dropwise. Reaction mixture was stirred at RT overnight, then was added NH_4Cl and diluted with DCM. Organic layer was dried over Na_2SO_4, filtered and solvent removed under reduced pressure. The crude was purified by preparative HPLC (H_2O/CH_3CN+0.1% TFA) to afford the title compound **D27** (45,8mg). Method 1: Rt=1.93min; m/z=432.4 $(M+H)^+$.

Description 28: 4-((2-(aminomethyl)piperidin-1-yl)sulfonyl)-N-(3,4-difluorophenyl)-3-fluoro-1-methyl-1H-pyrrole-2-carboxamide (D28)

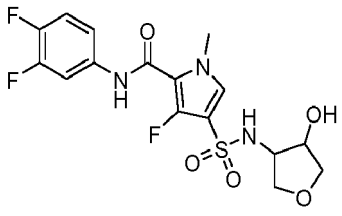
[0191]



[0192] To a suspension of **D13** (66.75mg, 0.17mmol) and 3,4-difluoroaniline (0.02mL, 0.21mmol) in dry THF (1.1mL), lithium bis(trimethylsilyl)amide 1M in THF (1.22mL, 1.22mmol) was added dropwise. Reaction mixture was stirred at RT overnight, then was added saturated NH_4Cl and diluted with DCM. Organic layer was dried over Na_2SO_4, filtered and solvent removed under reduced pressure to afford the title product **D28** in approximately 78% yield. Method 1: Rt= 1.43min. m/z=431.15 $(M+H)^+$

Description 29: trans N-(3,4-difluorophenyl)-3-fluoro-4-(N-(4-hydroxytetrahydrofuran-3-yl)sulfamoyl)-1-methyl-1H-pyrrole-2-carboxamide (D29)

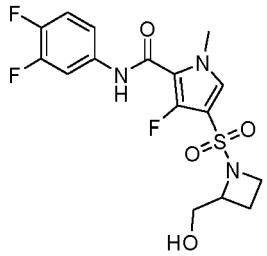
[0193]



[0194] To a suspension of **D15** (133mg, 0.0395mmol) and 3,4-difluoroaniline (0.05mL, 0.04mmol) in dry THF (0.7mL), lithium bis(trimethylsilyl)amide 1M in THF (2.27mL, 2.27mmol) was added dropwise. Reaction mixture was stirred at RT overnight. Volatiles were evaporated and the residue was crystallized from hot Petroleum ether and EtOAc affording the title compound **D29,** as a trans 3S4R and 3R4S racemate (139.5mg, y= 81%). Method 3: Rt= 2.74min. m/z=420.34 $(M+H)^+$

Description 30: N-(3,4-difluorophenyl)-3-fluoro-4-((2-(hydroxymethyl)azetidin-1-yl)sulfonyl)-1-methyl-1H-pyrrole-2-carboxamide (D30)

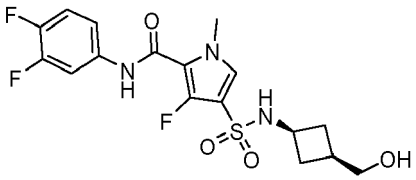
[0195]



[0196] To a suspension of **D14** (10.8mg, 0.03mmol) and 3,4-difluoroaniline (0.004mL, 0.04mmol) in dry THF (0.7mL), lithium bis(trimethylsilyl)amide 1M in THF (0.19mL, 0.19mmol) was added dropwise. Reaction mixture was stirred at RT for 30min, then was added saturated NH_4Cl and diluted with DCM. Organic layer was dried over Na_2SO_4, filtered and solvent removed under reduced pressure to afford the title compound **D30** in approximately quantitative yield (14mg). Method 1: Rt= 1.77min. m/z=404.26 $(M+H)^+$

Description 31: *cis*-N-(3,4-difluorophenyl)-3-fluoro-4-(N-(3-(hydroxymethyl)cyclobutyl)sulfamoyl)-1-methyl-1H-pyrrole-2-carboxamide (D31)

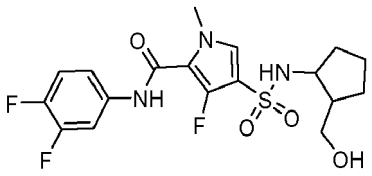
[0197]



[0198] To a solution of **D16** (45 mg, 0.135 mmol) and 3,4-difluoroaniline (0.016 mL, 0.161 mmol) in dry THF (0.8 mL), lithium bis(trimethylsilyl)amide 1M in THF (0.750 mL, 0.750 mmol) was added at room temperature. After 1.5 h lithium bis(trimethylsilyl)amide 1M in THF (0.300 mL, 0.300 mmol) and 3,4-difluoroaniline (0.005 mL, 0.050 mmol) were added to have complete conversion. Mixture was diluted with DCM and washed with 5% citric acid solution (x2). Organic layer was dried over Na_2SO_4, filtered and solvent removed under reduced pressure to afford a brown solid (83 mg). Crude was purified with preparative HPLC-MS (H_2O/CH_3CN +0.1% TFA) to give **D31** as pink powder (39.5 mg). ^1H NMR (300 MHz, DMSO-d_6) δ ppm 1.53 - 1.65 (m, 2 H) 1.89 - 2.03 (m, 1 H) 2.03 - 2.15 (m, 2 H) 3.23 - 3.29 (m, 3 H) 3.42 - 3.68 (m, 2 H) 3.80 (s, 3 H) 7.37 - 7.48 (m, 3 H) 7.78 - 7.89 (m, 2 H) 10.22 (s, 1 H). Method 3: Rt=2.94 min, m/z=418 $(M+H)^+$.

Description 32: cis-N-(3,4-difluorophenyl)-3-fluoro-4-(N-(2-(hydroxymethyl)cyclopentyl)sulfamoyl)-1-methyl-1H-pyrrole-2-carboxamide (D32)

[0199]

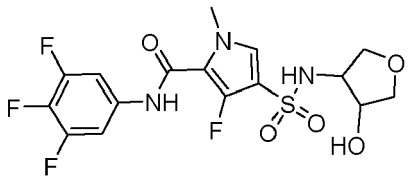


[0200] To a solution of **D17** (18 mg, 0.052 mmol) and 3,4-difluoroaniline (0.006 mL, 0.062 mmol) in dry THF (1 mL), lithium bis(trimethylsilyl)amide 1M in THF (0.360 mL, 0.360 mmol) was added at rt. After 30 minutes mixture was diluted with DCM and washed with 5% citric acid solution. Organic layer was dried over Na_2SO_4, filtered and solvent removed under reduced pressure to afford a brown solid. Crude was purified with preparative HPLC-MS (H_2O/CH_3CN +0.1%

TFA) to give **D32** as a white powder (12.5 mg, y=56%). The compound is the cis racemic mixture of 1S,2R and 1R,2S at the cyclopentyl ring. Method 1: Rt=1.89 min, m/z=432 $(M+H)^+$.

Description 33: trans-3-fluoro-4-(N-(4-hydroxytetrahydrofuran-3-yl)sulfamoyl)-1-methyl-N-(3,4,5-trifluorophenyl)-1H-pyrrole-2-carboxamide (D33)

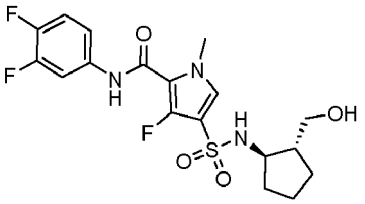
[0201]



[0202] To a solution of **D18** (70 mg, 0.208 mmol) and 3,4,5-trifluoroaniline (0.025 mL, 0.221 mmol) in dry THF (1.5 mL), lithium bis(trimethylsilyl)amide 1M in THF (1.2 mL, 1.2 mmol) was added at room temperature. After 45 min, the mixture was evaporated under reduced pressure to afford a light violet solid (204 mg). Crude was purified with preparative HPLC-MS (H_2O/CH_3CN +0.1% TFA) to give **D33** as a white powder (42.3 mg, y= 46%). The compound is the trans racemic mixture of 3S,4R and 3R,4S at the tetrahydrofuranyl ring. ^1H NMR (300 MHz, DMSO-d_6 +TFA) δ ppm 3.43 - 3.60 (m, 1 H) 3.45 - 3.49 (m, 1 H) 3.52 - 3.58 (m, 1 H) 3.77 - 3.86 (m, 5 H) 4.07 - 4.12 (m, 1 H) 7.49 - 7.66 (m, 3 H) 7.95 (br d, J=4.77 Hz, 1 H) 10.34 (s, 1 H). Method 3: Rt=2.98 min, m/z=438 $(M+H)^+$.

Description 34: N-(3,4-difluorophenyl)-3-fluoro-4-(N-((1R,2R)-2-(hydroxymethyl)cyclopentyl)sulfamoyl)-1-methyl-1H-pyrrole-2-carboxamide (D34)

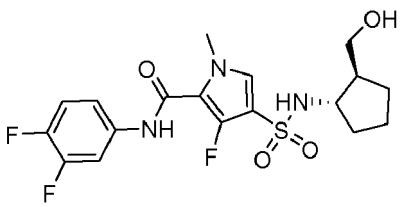
[0203]



[0204] To a solution of **D1**9 (59 mg, 0.169 mmol) and 3,4-difluoroaniline (0.020 mL, 0.203 mmol) in dry THF (1.5 mL), lithium bis(trimethylsilyl)amide 1M in THF (0.850 mL, 0.850 mmol) was added at room temperature. After 40 min UPLC-MS analysis showed conversion was not completed so (3,4-Difluoroaniline (0.010 mL, 0.101 mmol) and lithium bis(trimethylsilyl)amide 1M in THF (0.400 ml, 0.400 mmol) were added. 30 minutes after the addition mixture was diluted with DCM and washed with 5% citric acid solution. Organic layer was dried over Na_2SO_4, filtered, solvent removed under reduced pressure to afford a brown solid (118 mg). Crude was purified with preparative HPLC-MS (H_2O/CH_3CN +0.1% TFA) to give **D34** as a white powder (44.7 mg). Method 1: Rt=1.90 min, m/z= 432 $(M+H)^+$.

Description 35: N-(3,4-difluorophenyl)-3-fluoro-4-(N-((1S,2S)-2-(hydroxymethyl)cyclopentyl)sulfamoyl)-1-methyl-1H-pyrrole-2-carboxamide (D35)

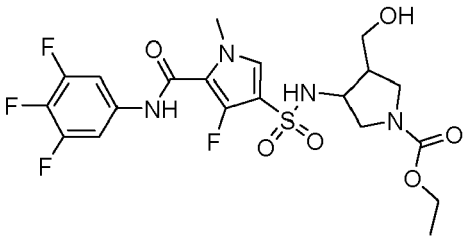
[0205]



[0206] Prepared similarly as described for compound **D34** starting from **D20.** Method 1: Rt=1.90 min, m/z= 432 $(M+H)^+$.

Description 36: cis-Ethyl 3-((4-fluoro-1-methyl-5-((3,4,5-trifluorophenyl)carbamoyl)-1H-pyrrole)-3-sulfonamido)-4-(hydroxymethyl)pyrrolidine-1-carboxylate (D36)

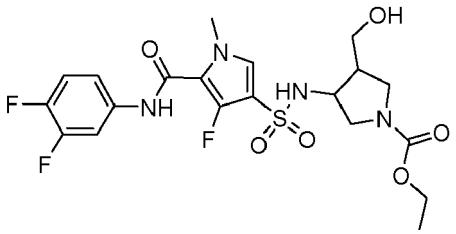
[0207]



[0208] To a solution of **D21** (101mg, 0.240 mmol) and 3,4,5-Trifluoroaniline (38.8 mg, 0.264 mmol) in dry THF (2 mL), lithium bis(trimethylsilyl)amide 1M in THF (1.2 mL, 1.2 mmol) was added at room temperature. After 1h 3,4,5-trifluoroaniline (20 mg, 0.136 mmol) and lithium bis(trimethylsilyl)amide 1M in THF (0.5 mL, 0.5 mmol) were added. Reaction was stopped after 2.5 h, mixture diluted with DCM and washed with 5% citric acid solution and water. Organic layer was dried over Na_2SO_4, filtered and solvent removed under reduced pressure. Crude was purified with flash chromatography (ETP/AcOEt) to afford **D36** as a brown solid (106 mg). The compound is the cis racemate at the pyrrolidine ring (racemate of 3S,4S and 3R,4R). Method 1: Rt=1.94 min, m/z= 523 $(M+H)^+$.

Description 37: cis-Ethyl 3-((5-((3,4-difluorophenyl)carbamoyl)-4-fluoro-1-methyl-1H-pyrrole)-3-sulfonamido)-4-(hydroxymethyl)pyrrolidine-1-carboxylate (D37)

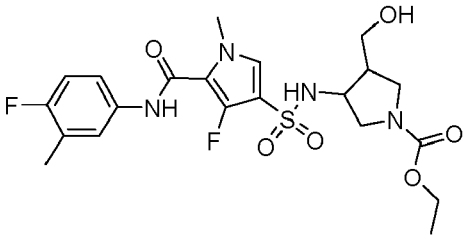
[0209]



[0210] Prepared similarly as described for compound **D36** using 3,4-difluoroaniline instead of 3,4,5-trifluoroaniline to give **D37.** The compound is the cis racemate at the pyrrolidine ring (racemate of 3S,4S and 3R,4R). Method 1: Rt=1.82 min, m/z=505 $(M+H)^+$.

Description 38: cis-Ethyl 3-((4-fluoro-5-((4-fluoro-3-methylphenyl)carbamoyl)-1-methyl-1H-pyrrole)-3-sulfonamido)-4-(hydroxymethyl)pyrrolidine-1-carboxylate (D38)

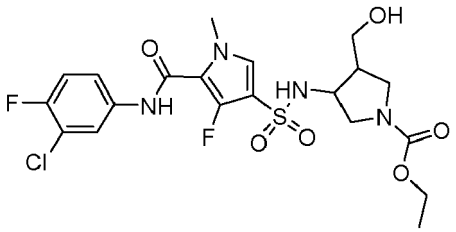
[0211]



[0212] Prepared similarly as described for compound **D36** using 4-fluoro-3-methylaniline instead of 3,4,5-trifluoroaniline to give **D38.** The compound is the cis racemate at the pyrrolidine ring (racemate of 3S,4S and 3R,4R). Method 1: Rt=1.83 min, m/z=501 $(M+H)^+$.

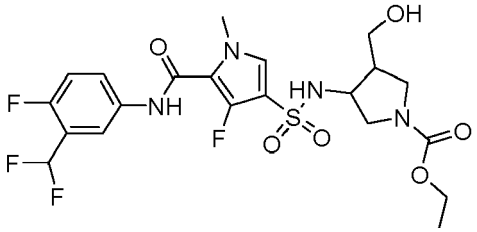
Description 39: cis-Ethyl 3-((5-((3-chloro-4-fluorophenyl)carbamoyl)-4-fluoro-1-methyl-1H-pyrrole)-3-sulfonamido)-4-(hydroxymethyl)pyrrolidine-1-carboxylate (D39)

[0213]



[0214] Prepared similarly as described for compound **D36** using 3-chloro-4-fluoroaniline, instead of 3,4,5-trifluoroaniline to give **D39.** The compound is the cis racemate at the pyrrolidine ring (racemate of 3S,4S and 3R,4R). Method 1: Rt=1.91min, m/z=521 $(M+H)^+$.

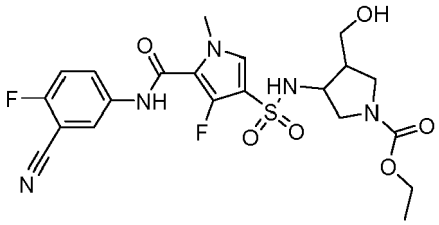
[0215] Description 40: cis-Ethyl 3-((5-((3-(difluoromethyl)-4-fluorophenyl)carbamoyl)-4-fluoro-1-methyl-lH-pyrrole)-3-sulfonamido)-4-(hydroxymethyl)pyrrolidine-1-carboxylate (D40)



[0216] Prepared similarly as described for compound **D36** using 3-(difluoromethyl)-4-fluoroaniline, instead of 3,4,5-trifluoroaniline to give **D40.** The compound is the cis racemate at the pyrrolidine ring (racemate of 3S,4S and 3R,4R). Method 1: Rt=1.84 min, m/z=537 $(M+H)^+$.

Description 41: cis-Ethyl 3-((5-((3-cyano-4-fluorophenyl)carbamoyl)-4-fluoro-1-methyl-1H-pyrrole)-3-sulfonamido)-4-(hydroxymethyl)pyrrolidine-1-carboxylate (D41)

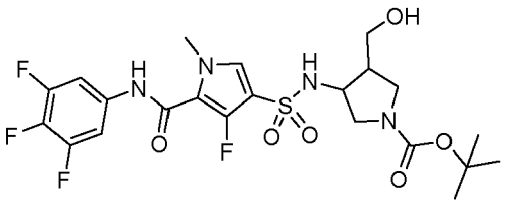
[0217]



[0218] Prepared similarly as described for compound **D36** using 5-amino-2-fluorobenzonitrile instead of 3,4,5-trifluoroaniline to give **D41.** The compound is the cis racemate at the pyrrolidine ring (racemate of 3S,4S and 3R,4R). Method 1: Rt=1.75 min, m/z=512 $(M+H)^+$.

Description 42 : cis-tert-butyl 3-((4-fluoro-1-methyl-5-((3,4,5-trifluorophenyl)carbamoyl)-1H-pyrrole)-3-sulfonamido)-4-(hydroxymethyl)pyrrolidine-1-carboxylate (D42)

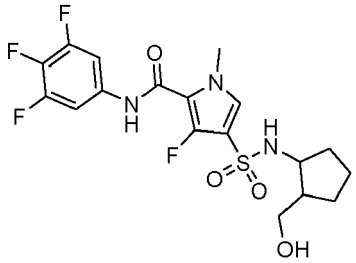
[0219]



[0220] To a suspension of **D22** (50mg, 0.11mmol) and 3,4,5-Trifluoroaniline (32.7mg, 0.22mmol) in dry THF (1mL), lithium bis(trimethylsilyl)amide 1M in THF (0.67mL, 0.67mmol) was added dropwise. Reaction mixture was stirred at RT for 1h, then was diluted with DCM and washed with 5% citric acid solution and water. Organic layer was dried over Na_2SO_4, filtered and solvent removed under reduced pressure to afford crude **D42** compound as orange oil (85mg, y>100%), that was used without further purification. The compound is the cis racemate at the pyrrolidine ring.

Description 43: cis-3-fluoro-4-(N-(2-(hydroxymethyl)cyclopentyl)sulfamoyl)-1-methyl-N-(3,4,5-trifluorophenyl)-1H-pyrrole-2-carboxamide (D43)

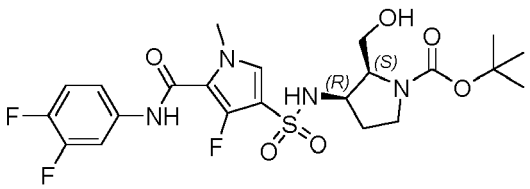
[0221]



[0222] Prepared similarly as described for compound **D32** starting from **D17** (52mg, 0.149mmol, 1eq) and 3,4,5-trifluoroaniline (27mg, 0.184mmol, 1.23eq) to give crude **D43** (66.9mg). Product was used without any purification. Method 1: Rt=2.06 min, m/z=450 $(M+H)^+$. The compound is the cis racemate at the cyclopentyl ring.

Description 44: tert-butyl (2S,3R)-3-((5-((3,4-difluorophenyl)carbamoyl)-4-fluoro-1-methyl-1H-pyrrole)-3-sulfonamido)-2-(hydroxymethyl)pyrrolidine-1-carboxylate (D44)

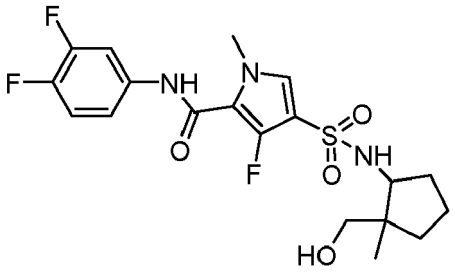
[0223]



[0224] **D23** (117.51mg, 0.261mmol, 1eq) was dissolved in THF (1.5mL, 0.174M), 3,4-difluoroaniline (34uL, 0.343mmol, 1.31eq) was added and 1M solution of lithium bis(trimethylsilyl)amide in THF (1.5mL, 1.5mmol, 5.74eq) was added dropwise. Reaction mixture was stirred at rt and complete conversion was observed after 35min. Reaction mixture was diluted with DCM, organic layer was washed with 5% aqueous citric acid solution, dried over sodium sulfate, filtered and solvent was removed under reduced pressure to afford **(D44)** as a crude product (141mg). Method 1: Rt=2.09 min; m/z=523 $(M+H)^+$.

Description 45: N-(3,4-difluorophenyl)-3-fluoro-4-(N-(2-(hydroxymethyl)-2-methylcyclopentyl)sulfamoyl)-1-methyl-1H-pyrrole-2-carboxamide (D45)

[0225]

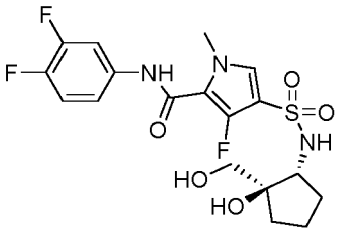


[0226] **D24** (70 mg, 0.193 mmol) was suspended in dry THF (2 mL) under a nitrogen atmosphere and 3,4-difluoroaniline (21 uL, 0.212 mmol, 1.1 eq) was added. LiHMDS 1M in THF (0.966 mL; 0.966 mmol, 5 eq) was added dropwise to the resulting pale yellow solution. The reaction turned dark red and was stirred at rt for 1h, until complete conversion. The reaction was diluted with DCM and washed with 5% citric acid (2x); the organic phase was dried over Na_2SO_4 and evaporated, yielding 114 mg of crude **D45** as a brown gum, used without further purification.

[0227] Method 1: Rt=1.70 min, m/z=363 $(M+H)^+$

Description 46: N-(3,4-difluorophenyl)-3-fluoro-4-(N-((1R,2R and 1S,2S)-2-hydroxy-2-(hydroxymethyl)cyclopentyl)sulfamoyl)-1-methyl-1H-pyrrole-2-carboxamide (D46)

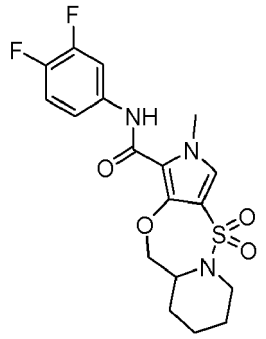
[0228]



[0229] Crude **D26** (21 mg, 0.058 mmol) was suspended in dry THF (1 mL) under a nitrogen atmosphere; 3,4-difluoroaniline (7 uL, 0.066 mmol, 1.15 eq) was added and to the resulting solution LiHMDS 1M in THF (0.288 mL; 0.288 mmol, 5 eq) was added. The reaction turned dark red and was stirred at rt for 2h: almost complete conversion. The reaction was diluted with DCM and washed with 5% citric acid; the organic phase was dried over Na_2SO_4 and evaporated, yielding 38mg (greater than the theorethical amount) of crude **D46** as a dark brown gum, used without further purification. Method 1: Rt=1.71 min, m/z=448 $(M+H)^+$.

Example 1: N-(3,4-difluorophenyl)-2-methyl-6,7,8,9,9a,10-hexahydro-2H-pyrido[1,2-e]pyrrolo[3,4-b][1,4,5]oxathiazepine-1-carboxamide4,4-dioxide (E1)

[0230]



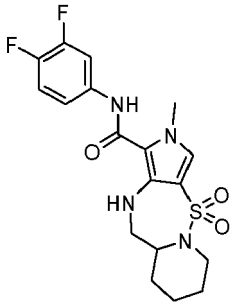
[0231] **D27** (35.77mg,0.080mmol) and cesium carbonate (54.36mg,0.170mmol) in DMF (0.543mL,0.007mol) were heated at 130°C for 45 min under microwave irradiation. A saturated aqueous ammonium chloride solution was added to the reaction mixture, and the mixture was extracted twice with ethyl acetate. The organic layer was washed with

NH_4Cl, dried over Na_2SO_4, and concentrated in vacuo. The resulting crude was purified by preparative HPLC (H_2O/CH_3CN +0.1% TFA) to afford the title compound **E1**, ^1H NMR (300 MHz, DMSO-d_6, 25°C): δ = 9.51 (s, 1H), 7.76-7.95 (m, 1H), 7.33-7.56 (m, 3H), 4.44-4.65 (m, 1H), 4.27-4.44 (m, 2H), 3.83 (s, 3H), 3.36-3.43 (m, 1H), 2.68-2.90 (m, 1H), 1.64-1.89 (m, 3H), 1.41-1.62 (m, 2H), 1.24 ppm (s, 1H).

[0232] Method 3: Rt=3.80min. m/z=412.17 $(M+H)^+$

Example 2: N-(3,4-difluorophenyl)-2-methyl-2,6,7,8,9,9a,10,11-octahydropyrido[1,2-b]pyrrolo[3,4-f][1,2,5]thiadiazepine-1-carboxamide 4,4-dioxide (E2)

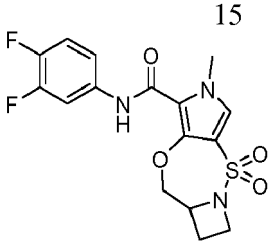
[0233]



[0234] **D28** (47.96mg,0.090mmol) and cesium carbonate (115.51mg,0.350mmol) in DMSO (1.3mL,0.018mol) were heated at 160°C for 7h under microwave irradiation. The reaction mixture was filtered, and the filtrate was purified by preparative HPLC (H_2O/CH_3CN +0.1% TFA) to afford the title compound **E2.** ^1H NMR (300 MHz, DMSO-d_6, 25°C): δ = 10.77-10.95 (m, 1H), 7.80 (ddd, *J* = 13.0, 7.5, 2.2 Hz, 1H), 7.19-7.58 (m, 3H), 5.15 (br t, *J*= 4.9 Hz, 1H), 4.08 (br d, *J* = 9.1 Hz, 1H), 3.70-3.87 (m, 3H), 3.36-3.48 (m, 1H), 3.09 (br dd, *J*= 14.8, 2.8 Hz, 1H), 2.67-2.80 (m, 1H), 1.61-1.80 (m, 3H), 1.27-1.59 ppm (m, 3H). Method 3: Rt=3.80min. m/z=411.29 $(M+H)^+$

Example 3: N-(3,4-difluorophenyl)-2-methyl-6,7,7a,8-tetrahydro-2H-azeto[1,2-e]pyrrolo[3,4-b][1,4,5]oxathiazepine-1-carboxamide 4,4-dioxide (E3)

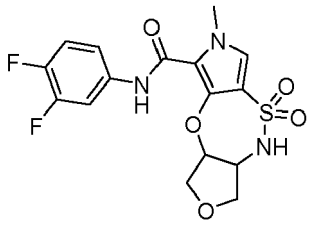
[0235]



[0236] **D30** (13.71mg,0.030mmol) and cesium carbonate (22.29mg,0.07mmol) in DMF (0.7 mL,0.009mol) were heated at 130°C for 1h under microwave irradiation. A saturated NH_4Cl solution was added to the reaction mixture, and the mixture was extracted twice with ethyl acetate. The organic layer was washed with saturated brine, dried over Na_2SO_4, and concentrated in vacuo. The resulting crude was purified by preparative HPLC (H_2O/CH_3CN+0.1% TFA) to afford the title compound **E3.** ^1H NMR (300 MHz, DMSO-d_6, 25°C): δ = 9.37-9.53 (m, 1H), 7.88 (ddd, *J* = 13.3, 7.5, 1.7 Hz, 1H), 7.54 (s, 1H), 7.37-7.51 (m, 2H), 4.87 (dd, *J*= 14.0, 0.9 Hz, 1H), 4.55 (dd, *J* = 14.1, 1.7 Hz, 1H), 4.48 (br dd, *J* = 8.8, 4.4 Hz, 1H), 3.85 (s, 3H), 3.69-3.83 ppm (m, 2H). Method 3: Rt= 3.46min. m/z=383.93 $(M+H)^+$

Example 4: *trans*-N-(3,4-difluorophenyl)-7-methyl-1,3a,4,9a-tetrahydro-3H,7H-furo[3,4-f]pyrrolo[3,4-b][1,4,5]oxathiazepine-8-carboxamide 5,5-dioxide (E4)

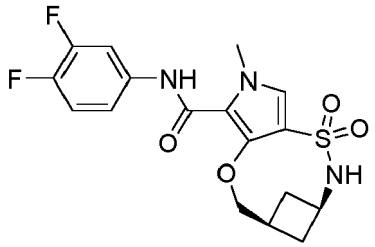
[0237]



[0238] Compound **D29** (114.5mg,0.27mmol) and cesium carbonate (179mg,0.55mmol) in DMF (1.8 mL,0.024mol) were heated at 150°C for 2h under microwave irradiation. A saturated NH_4Cl solution was added to the reaction mixture, and the mixture was extracted twice with ethyl acetate. The organic layer was washed with saturated brine, dried over Na_2SO_4, and concentrated in vacuo. The resulting crude was purified by preparative HPLC (H_2O/CH_3CN +0.1% TFA) to afford the title compound **E4.** The compound is the trans racemate (3aS,9aR and 3aR,9aS). ^1H NMR (300 MHz, DMSO-d_6, 25°C): δ = 9.51 (s, 1H), 7.95 (d, *J*= 10.5 Hz, 1H), 7.84 (ddd, *J*= 13.2, 7.5, 2.1 Hz, 1H), 7.58 (s, 1H), 7.29-7.49 (m, 2H), 4.56 (q, *J* = 8.0 Hz, 1H), 4.06-4.36 (m, 3H), 3.89 (t, *J* = 8.6 Hz, 1H), 3.79-3.85 (m, 3H), 3.58-3.62 ppm (m, 1H). Method 3: Rt= 3.22min. m/z=400.01 $(M+H)^+$

Example 5: *cis*-N-(3,4-difluorophenyl)-9-methyl-3,4,5,6-tetrahydro-2H,9H-3,5-methanopyrrolo[3,4-b][1,4,5]oxathiazonine-8-carboxamide 1,1-dioxide (E5)

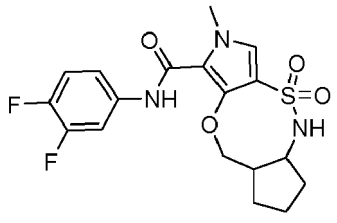
[0239]



[0240] In a microwave vial **D31** (30.5 mg, 0.073 mmol) was dissolved in dry DMF (1.5 mL); cesium carbonate (60 mg, 0.184 mmol) was added, the vial was sealed and mixture heated under microwave irradiations for 8h at 150°C. Crude was purified with preparative HPLC-MS (H_2O/CH_3CN +0.1% TFA) to give **E5** a pale pink powder (5.38 mg). ^1H NMR (300 MHz, DMSO-**d_6**) δ ppm 2.31 - 2.45 (m, 3 H) 2.55 - 2.68 (m, 2 H) 3.80 (s, 5 H) 3.99 (s, 2 H) 7.34 (d, J=2.48 Hz, 1 H) 7.37 - 7.46 (m, 2 H) 7.46 - 7.53 (m, 1 H) 7.86 (br dd, J=7.57, 2.52 Hz, 1 H) 7.90 (br dd, J=7.57, 2.43 Hz, 1 H) 9.99 (s, 1 H). Method 3: Rt=3.22 min, m/z=398 $(M+H)^+$.

Example 6: *cis*-N-(3,4-difluorophenyl)-2-methyl-5a,6,7,8,8a,9-hexahydro-2H,5H-cyclopenta[f]pyrrolo[3,4-b][1,4,5]oxathiazocine-1-carboxamide 4,4-dioxide (E6)

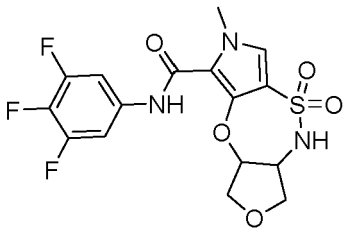
[0241]



[0242] In a microwave vial **D32** (10 mg, 0.023 mmol) was dissolved in dry DMF (1 mL); cesium carbonate (19.5 mg, 0.060 mmol) was added, the vial sealed and mixture heated at 130° for 40 min. Crude was purified with preparative HPLC-MS (H_2O/CH_3CN+0.1% TFA) to give **E6** a white powder (5.37 mg). The compound is the cis racemate (5aS,8aR and 5aR,8aS). ^1H NMR (300 MHz, DMSO-d_6) δ ppm 1.11 - 1.30 (m, 1 H) 1.39 - 1.78 (m, 4 H) 2.01 - 2.17 (m, 1 H) 3.76 - 3.95 (m, 4 H) 4.20 - 4.34 (m, 1 H) 4.49 (dd, *J*=11.28, 4.49 Hz, 1 H) 7.32 - 7.53 (m, 3 H) 7.81 - 7.95 (m, 2 H) 9.55 (s, 1 H). Method 3: Rt= 3.68 min, m/z=412 $(M+H)^+$.

Example 7: *trans*-7-methyl-N-(3,4,S-trifluorophenyl)-1,3a,4,9a-tetrahydro-3H,7H-furo[3,4-f]pyrrolo[3,4-b][1,4,5]oxathiazepine-8-carboxamide 5,5-dioxide (E7)

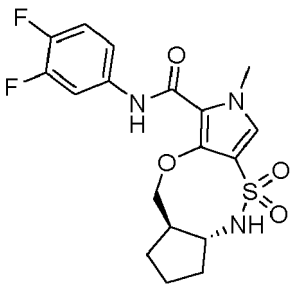
[0243]



[0244] In a microwave vial **D33** (40 mg, 0.091 mmol) was dissolved in dry DMF (2 mL); cesium carbonate (74.5 mg, 0.229 mmol) was added, the vial was sealed and mixture heated 3h at 130°C under microwave heating. Mixture was purified with preparative HPLC-MS (H_2O/CH_3CN +0.1% TFA) to give **E7** a white powder (11.26 mg). The compound is the trans racemate (3aS,9aR and 3aR,9aS). ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 3.50 - 3.63 (m, 1 H) 3.82 (s, 3 H) 3.91 (t, *J*=8.67 Hz, 1 H) 4.06 - 4.33 (m, 3 H) 4.55 (q, *J*=7.89 Hz, 1 H) 7.55 - 7.65 (m, 3 H) 7.96 (d, *J*=10.36 Hz, 1 H) 9.60 (s, 1 H). Method 3: Rt=3.44 min, m/z=418 $(M+H)^+$.

Example 8: (5aR,8aR)-N-(3,4-difluorophenyl)-2-methyl-5a,6,7,8,8a,9-hexahydro-2H,5H-cyclopenta[f]pyrrolo[3,4-b][1,4,5]oxathiazocine-1-carboxamide 4,4-dioxide (E8)

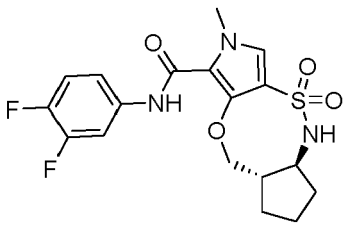
[0245]



[0246] In a microwave vial **D34** (40 mg, 0.093 mmol) was dissolved in dry DMF (2 mL); cesium carbonate (75.5 mg, 0.232 mmol) was added, the vial was sealed and mixture heated at 130°C under MW for 40 min. Mixture was purified with preparative HPLC-MS (H_2O/CH_3CN +0.1% TFA) to afford **E8** a white powder (26.47 mg). ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 1.07 (br d, *J*=7.70 Hz, 1 H) 1.37 - 1.69 (m, 4 H) 2.00 - 2.23 (m, 2 H) 3.77 - 3.98 (m, 6 H) 7.27 (d, *J*=10.45 Hz, 1 H) 7.36 - 7.50 (m, 3 H) 7.87 (ddd, *J*=13.20, 7.47, 2.25 Hz, 1 H) 9.83 (s, 1 H). Method 3: Rt=3.55 min, m/z=412 $(M+H)^+$.

Example 9: (5aS,8aS)-N-(3,4-difluorophenyl)-2-methyl-5a,6,7,8,8a,9-hexahydro-2H,5H-cyclopenta[f]pyrrolo[3,4-b][1,4,5]oxathiazocine-1-carboxamide 4,4-dioxide (E9)

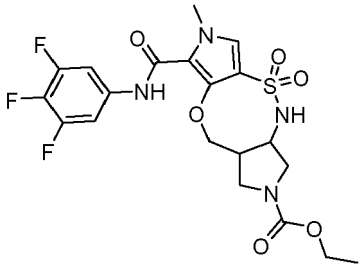
[0247]



[0248] Prepared similarly as described for compound **E8** starting from **D35** to give **E9.** ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 1.02 - 1.16 (m, 1 H) 1.32 - 1.72 (m, 1 H) 2.00 - 2.27 (m, 2 H) 3.76 - 4.00 (m, 6 H) 7.27 (d, J=10.55 Hz, 1 H) 7.35 - 7.51 (m, 3 H) 7.87 (ddd, J=13.20, 7.47, 2.15 Hz, 1 H) 9.83 (s, 1 H). Method 3: Rt=3.55 min, m/z=412 $(M+H)^+$.

Example 10: *cis*-Ethyl 7-methyl-8-((3,4,5-trifluorophenyl)carbamoyl)-3a,4,10,10a-tetrahydro-1H,7H-dipyrrolo[3,4-b:3',4'-f][1,4,5]oxathiazocine-2(3H)-carboxylate 5,5-dioxide (E10)

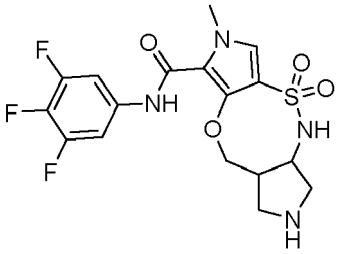
[0249]



[0250] In a microwave vial **D36** (106 mg, 0.203 mmol) was dissolved in dry DMF (5 mL); cesium carbonate (166 mg, 0.509 mmol) was added, the vial was sealed and mixture heated at 130°C under MW for 70 min. Mixture was filtered and solvent removed under reduced pressure to afford a beige solid (152 mg). Crude was purified with preparative HPLC-MS (H_2O/CH_3CN+0.1% TFA) to afford **E10** a white powder (79.4mg). The compound is the cis racemate at the pyrrolidine ring (racemate of 3aR,10aR and 3aS,10aS). ^{1}H NMR (300 MHz, DMSO-d_6+TFA) δ ppm 1.12 - 1.22 (m, 3 H) 2.91 - 3.14 (m, 2 H) 3.33 - 3.46 (m, 2 H) 3.62 - 3.76 (m, 1 H) 3.79 (s, 3 H) 3.83 - 3.96 (m, 1 H) 4.02 (q, J=7.06 Hz, 2 H) 4.38 - 4.48 (m, 1 H) 4.48 - 4.62 (m, 1 H) 7.49 (s, 1 H) 7.62 - 7.73 (m, 2 H) 8.41 (br d, J=9.72 Hz, 1 H) 9.64 (s, 1 H). Method 3: Rt=3.57 min, m/z=503 $(M+H)^+$.

Example 11: *cis*- 7-methyl-N-(3,4,5-trifluorophenyl)-2,3,3a,4,10,10a-hexahydro-1H,7H-dipyrrolo[3,4-b:3',4'-f][1,4,5]oxathiazocine-8-carboxamide 5,5-dioxide (E11)

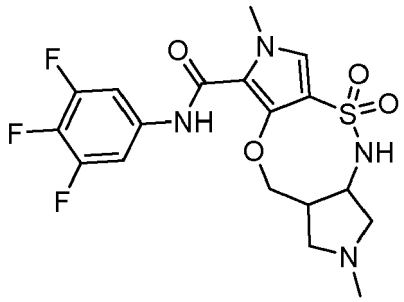
[0251]



[0252] In a sealed microwave vial, **E10** (185.5 mg, 0.369 mmol) was dissolved in dry DCM (2 mL). Trimethylsilyl iodide (1.1 mL, 7.6965 mmol) was added and mixture was heated at 50°C. After 4.5h even if conversion was not completed, crude was evaporeted under reduced pressure to afford a brown solid (350 mg). Then it was triturated with Et_2O and filtered. Brown solid was dried at vacuum pump (232 mg) and it was used without any further purification. Part of crude was purified with preparative HPLC-MS (H_2O/CH_3CN +0.1% TFA) to afford **E11** a white powder (15.65 mg). The compound is the cis racemate at the pyrrolidine ring (mixture of 3aR,10aR and 3aS,10aS). ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 2.82 - 3.02 (m, 2 H) 3.08 - 3.22 (m, 1 H) 3.81 (s, 4 H) 3.88 - 4.05 (m, 1 H) 4.54 - 4.66 (m, 2 H) 7.55 (s, 1 H) 7.64 - 7.74 (m, 2 H) 8.38 (d, J=9.90 Hz, 1 H) 8.97 (br s, 2 H) 9.68 (s, 1 H). Method 3: Rt=2.50 min, m/z=431 $(M+H)^+$.

Example 12: *cis*-2,7-dimethyl-N-(3,4,5-trifluorophenyl)-2,3,3a,4,10,10a-hexahydro-1H,7H-dipyrrolo[3,4-b:3',4'-f][1,4,5]oxathiazocine-8-carboxamide 5,5-dioxide (E12)

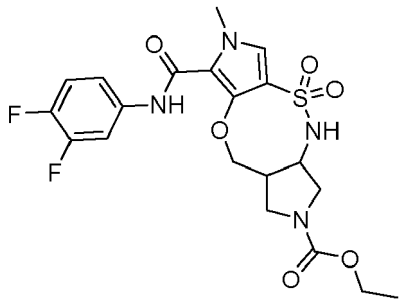
[0253]



[0254] **E11** (7.2 mg, 0.017 mmol) was dissolved in 1 mL of a solution composed by MeOH (10 mL), formaldehyde 37% aq. (0.170 mL, 2.285 mmol) and acetic acid (0.030 mL, 0.506 mmol) at room temperature. After 10 minutes, sodium triacetyloxyborohydride (7.5 mg, 0.035 mmol) was added and the reaction mixture was stirred at room temperature. Further aliquots of formaldehyde and acetic acid were added until UPLC-MS analysis showed complete conversion. Crude was purified with preparative HPLC-MS (H2O/CH3CN+0.1% TFA) to afford **E12** as a white powder (3.87 mg). The compound is the cis racemate at the pyrrolidine ring (mixture of 3aR,10aR and 3aS,10aS). ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 2.79 - 3.07 (m, 5 H) 3.15 - 3.39 (m, 1 H) 3.49 - 3.74 (m, 1 H) 3.80 (s, 3 H) 3.93 - 4.11 (m, 1 H) 4.15 - 4.31 (m, 1 H) 4.51 - 4.76 (m, 2 H) 7.50 (s, 1 H) 7.67 (br dd, J=10.04, 6.56 Hz, 2 H) 8.17 - 8.32 (m, 1 H) 0.00 (d, J=9.20 Hz, 1 H) 9.56 - 9.77 (m, 1 H) 10.20 (br s, 1 H). Method 3: Rt=2.57 min, m/z=445 (M+H)+.

Example 13: *cis*-Ethyl 8-((3,4-difluorophenyl)carbamoyl)-7-methyl-3a,4,10,10a-tetrahydro-1H,7H-dipyrrolo[3,4-b:3',4'-f][1,4,5]oxathiazocine-2(3H)-carboxylate 5,5-dioxide (E13)

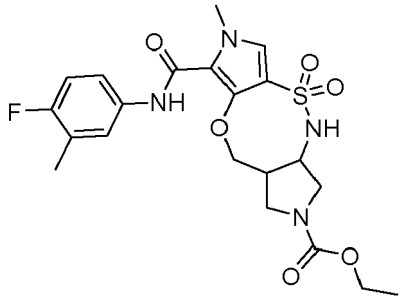
[0255]



[0256] Prepared similarly as described for compound **E10** starting from **D37** to give **E13.** The compound is the cis racemate at the pyrrolidine ring (racemate of 3aR,10aR and 3aS,10aS). ^{1}H NMR (300 MHz, DMSO-d_6+TFA) δ ppm 1.12 - 1.22 (m, 3 H) 2.91 - 3.15 (m, 2 H) 3.31 - 3.49 (m, 2 H) 3.66 - 3.86 (m, 4 H) 3.91 (br t, J=11.05 Hz, 1 H) 4.02 (q, J=6.97 Hz, 2 H) 4.38 - 4.51 (m, 1 H) 4.51 - 4.65 (m, 1 H) 7.29 - 7.51 (m, 3 H) 7.85 (ddd, J=13.14, 7.50, 2.29 Hz, 1 H) 8.41 (br d, J=9.72 Hz, 1 H) 9.55 (s, 1 H). Method 3: Rt=3.38 min, m/z=485 $(M+H)^+$.

Example 14: *cis*-Ethyl 8-((4-fluoro-3-methylphenyl)carbamoyl)-7-methyl-3a,4,10,10a-tetrahydro-1H,7H-dipyrrolo[3,4-b:3',4'-f][1,4,5]oxathiazocine-2(3H)-carboxylate 5,5-dioxide (E14)

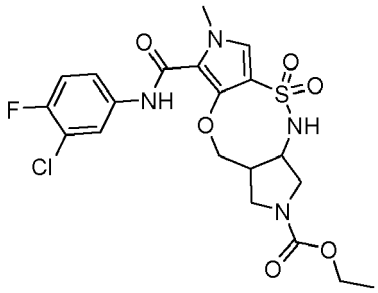
[0257]



[0258] Prepared similarly as described for compound **E10** starting from **D38** to give **E14.** The compound is the cis racemate at the pyrrolidine ring (racemate of 3aR,10aR and 3aS,10aS). ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 1.14 - 1.24 (m, 3 H) 2.24 (d, J=1.56 Hz, 3 H) 2.91 - 3.14 (m, 2 H) 3.33 - 3.42 (m, 2 H) 3.67 - 3.85 (m, 4 H) 3.91 (br t, J=10.87 Hz, 1 H) 4.03 (q, J=7.12 Hz, 2 H) 4.44 (br s, 1 H) 4.57 (br s, 1 H) 7.11 (t, J=9.22 Hz, 1 H) 7.45 - 7.53 (m, 2 H) 7.59 (dd, J=7.02, 2.43 Hz, 1 H) 8.40 (br d, J=9.54 Hz, 1 H) 9.34 (s, 1 H). Method 3: Rt=3.40 min, m/z=481 $(M+H)^+$.

Example 15: *cis*-Ethyl 8-((3-chloro-4-fluorophenyl)carbamoyl)-7-methyl-3a,4,10,10a-tetrahydro-1H,7H-dipyrrolo[3,4-b:3',4'-f][1,4,5]oxathiazocine-2(3H)-carboxylate 5,5-dioxide (E15)

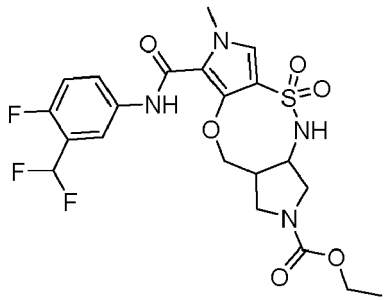
[0259]



[0260] Prepared similarly as described for compound **E10** starting from **D39** to give **E15.** The compound is the cis racemate at the pyrrolidine ring (mixture of 3aR,10aR and 3aS,10aS). ^{1}H NMR (300 MHz, DMSO-d6) δ ppm 1.14 - 1.24 (m, 3 H) 2.92 - 3.12 (m, 2 H) 3.32 - 3.42 (m, 2 H) 3.66 - 3.77 (m, 1 H) 3.81 (s, 3 H) 3.90 (br t, J=10.87 Hz, 1 H) 4.03 (q, J=7.03 Hz, 2 H) 4.39 - 4.49 (m, 1 H) 4.51 - 4.64 (m, 1 H) 7.41 (t, J=9.08 Hz, 1 H) 7.48 (s, 1 H) 7.61 - 7.67 (m, 1 H) 7.99 (dd, J=6.88, 2.57 Hz, 1 H) 8.41 (br d, J=9.81 Hz, 1 H) 9.57 (s, 1 H). Method 3: Rt= 3.54 min, m/z=501 $(M+H)^+$.

Example 16: *cis*-Ethyl 8-((3-(difluoromethyl)-4-fluorophenyl)carbamoyl)-7-methyl-3a,4,10,10a-tetrahydro-1H,7H-dipyrrolo[3,4-b:3',4'-f][1,4,5]oxathiazocine-2(3H)-carboxylate 5,5-dioxide (E16)

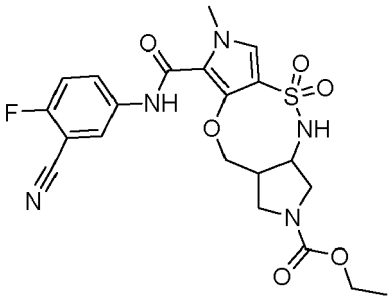
[0261]



[0262] Prepared similarly as described for compound **E10** starting from **D40** to give **E16.** The compound is the cis racemate at the pyrrolidine ring (racemate of 3aR,10aR and 3aS,10aS). ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 1.13 - 1.23 (m, 3 H) 2.91 - 3.14 (m, 2 H) 3.32 - 3.43 (m, 2 H) 3.71 (br dd, J=11.14, 5.82 Hz, 1 H) 3.81 (s, 3 H) 3.90 (br t, J=10.77 Hz, 1 H) 4.03 (q, J=7.03 Hz, 2 H) 4.39 - 4.49 (m, 1 H) 4.51 - 4.64 (m, 1 H) 7.03 - 7.43 (m, 2 H) 7.48 (s, 1 H) 7.76 - 7.83 (m, 1 H) 8.06 (dd, J=6.24, 2.38 Hz, 1 H) 8.41 (br d, J=10.00 Hz, 1 H) 9.63 (s, 1 H). Method 3: Rt= 3.38 min, m/z=517 $(M+H)^+$.

Example 17: *cis*-Ethyl 8-((3-cyano-4-fluorophenyl)carbamoyl)-7-methyl-3a,4,10,10a-tetrahydro-1H,7H-dipyrrolo[3,4-b:3',4'-f][1,4,5]oxathiazocine-2(3H)-carboxylate 5,5-dioxide (E17)

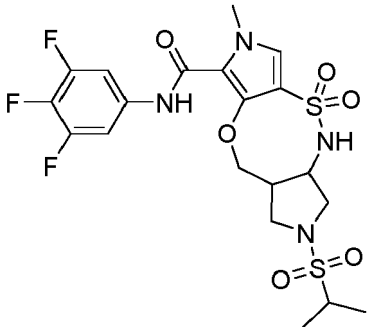
[0263]



[0264] Prepared similarly as described for compound **E10** starting from **D41** to give **E17.** The compound is the cis racemate at the pyrrolidine ring (mixture of 3aR,10aR and 3aS,10aS). ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 1.14 - 1.24 (m, 3 H) 2.92 - 3.14 (m, 2 H) 3.31 - 3.43 (m, 2 H) 3.72 (br dd, J=11.19, 5.87 Hz, 1 H) 3.81 (s, 3 H) 3.91 (br t, J=11.00 Hz, 1 H) 4.04 (q, J=6.97 Hz, 2 H) 4.38 - 4.50 (m, 1 H) 4.52 - 4.67 (m, 1 H) 7.49 - 7.57 (m, 2 H) 8.01 - 8.08 (m, 1 H) 8.19 (dd, J=5.73, 2.61 Hz, 1 H) 8.43 (br d, J=9.90 Hz, 1 H) 9.68 (s, 1 H). Method 3: Rt= 3.24 min, m/z=492 $(M+H)^+$.

Example 18: *cis*-2-(isopropylsulfonyl)-7-methyl-N-(3,4,5-trifluorophenyl)-2,3,3a,4,10,10a-hexahydro-1H,7H-dipyrrolo[3,4-b:3',4'-f][1,4,5]oxathiazocine-8-carboxamide 5,5-dioxide (E18)

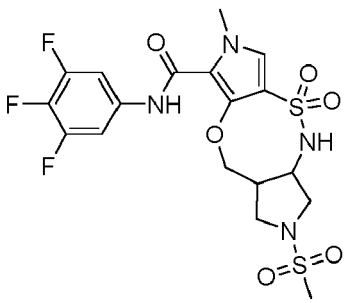
[0265]



[0266] To a suspension of **E11** (25 mg, 0.058 mmol) in dry DCM (0.5 mL) propane-2-sulfonyl chloride (0.007 mL, 0.062 mmol) and dry DIPEA (0.020 mL, 0.115 mmol) were added at room temperature. After 50 min, water (0.050 mL) was added and mixture was evaporated under reduced pressure. Crude was purified with preparative HPLC-MS (H_2O/CH_3CN +0.1% TFA) to give **E18** as a yellow powder (8.12 mg). The compound is the cis racemate at the pyrrolidine ring (racemate of 3aR,10aR and 3aS,10aS). ^{1}H NMR (300 MHz, DMSO-d_6+TFA) δ ppm 1.25 (d, *J*=6.79 Hz, 6 H) 2.98 - 3.13 (m, 2 H) 3.25 - 3.52 (m, 3 H) 3.76 - 3.99 (m, 5 H) 4.48 - 4.63 (m, 2 H) 7.51 (s, 1 H) 7.60 - 7.74 (m, 2 H) 8.48 (d, *J*=10.00 Hz, 1 H) 9.65 (s, 1 H). Method 3: Rt= 3.60 min, m/z=537 $(M+H)^+$.

Example 19: *cis*-7-methyl-2-(methylsulfonyl)-N-(3,4,5-trifluorophenyl)-2,3,3a,4,10,10a-hexahydro- 1H,7H-dipyrrolo[3,4-b:3',4'-f][1,4,5]oxathiazocine-8-carboxamide 5,5-dioxide (E19)

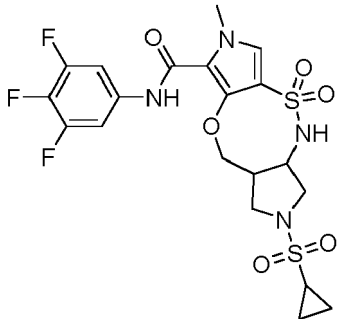
[0267]



[0268] To a suspension of **E11** (25 mg, 0.058 theoretical mmol) in dry acetonitrile (0.5 mL), methanesulfonyl chloride (5 ul, 0.065 mmol) and dry DIPEA (0.020 mL, 0.116 mmol) were added at room temperature. After 2h methanesulfonyl chloride (5 ul, 0.065 mmol) and dry DIPEA (0.020 mL, 0.116 mmol) were added. After 1h stirring, water (0.050 mL) was added and mixture evaporated under reduced pressure. Crude was purified by preparative HPLC-MS (H_2O/CH_3CN +0.1% TFA) to give **E19** as a pale orange powder (9.17 mg). The compound is the cis racemate at the pyrrolidine ring (racemate of 3aR,10aR and 3aS, 10aS).^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 2.92 (s, 3 H) 2.96 - 3.11 (m, 2 H) 3.19 - 3.31 (m, 1 H) 3.31 - 3.44 (m, 1 H) 3.72 - 3.85 (m, 4 H) 3.91 (t, *J*=11.00 Hz, 1 H) 4.48 - 4.60 (m, 2 H) 7.45 (s, 1 H) 7.60 - 7.72 (m, 2 H) 8.44 (d, *J*=9.90 Hz, 1 H) 9.72 (s, 1 H). Method 3: Rt= 3.34 min, m/z=509 $(M+H)^+$.

Example 20: *cis*-2-(cyclopropylsulfonyl)-7-methyl-N-(3,4,5-trifluorophenyl)-2,3,3a,4,10,10a-hexahydro-1H,7H-dipyrrolo[3,4-b:3',4'-f][1,4,5]oxathiazocine-8-carboxamide 5,5-dioxide (E20)

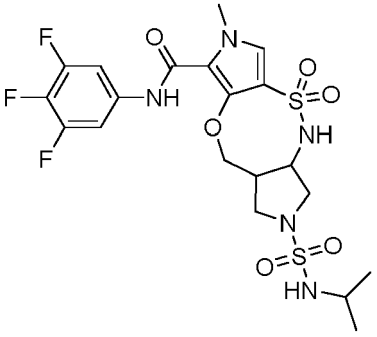
[0269]



[0270] To a suspension of **E11** (25 mg, 0.058 theoretical mmol) in dry acetonitrile (0.5 mL), cyclopropanesulfonyl chloride(7 ul, 0.069 mmol) and dry DIPEA (0.020 mL, 0.116 mmol) were added at room temperature and mixture stirred for 1.5h. First purification with preparative HPLC-MS (H_2O/CH_3CN +0.1% TFA) was not enough to obtained a purity >95%, so a second purification was performed by flash chromatography (DCM/AcOEt) and a white powder was afford **E20** (4.13 mg). The compound is the cis racemate at the pyrrolidine ring (racemate of 3aR,10aR and 3aS,10aS). ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 0.91 - 1.04 (m, 4 H) 2.63 - 2.75 (m, 1 H) 2.98 - 3.13 (m, 2 H) 3.28 (dd, J=10.68, 1.79 Hz, 1 H) 3.39 - 3.52 (m, 1 H) 3.78 - 3.89 (m, 4 H) 3.94 (br t, *J*=10.96 Hz, 1 H) 4.50 - 4.61 (m, 2 H) 7.50 (s, 1 H) 7.60 - 7.75 (m, 2 H) 8.44 (d, J=10.00 Hz, 1 H) 9.66 (s, 1 H). Method 3: Rt= 3.53 min, m/z=535 $(M+H)^+$.

Example 21: *cis*-2-(N-isopropylsulfamoyl)-7-methyl-N-(3,4,5-trifluorophenyl)-2,3,3a,4,10,10a-hexahydro-1H,7H-dipyrrolo[3,4-b:3',4'-f][1,4,5]oxathiazocine-8-carboxamide 5,5-dioxide (E21)

[0271]

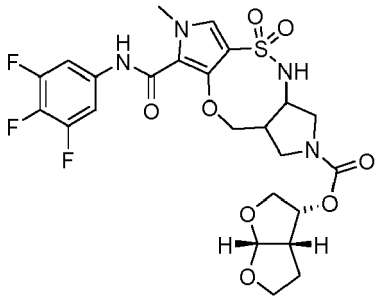


[0272] To a suspension of **E11** (25 mg, 0.058 mmol) in dry acetonitrile (0.5 mL), isopropylsulfamyl chloride (7.5 ul, 0.063 mmol) and dry DIPEA (0.025 mL, 0.144 mmol) were added at room temperature. After 1h conversion was not completed so, dry DIPEA (0.025 mL, 0.144 mmol) and isopropylsulfamyl chloride (7.5 ul, 0.063 mmol) were added. After a total of 4h water (0.050 mL) was added and mixture evaporated under reduced pressure. Crude was purified with preparative HPLC-MS (H_2O/CH_3CN +0.1% TFA) to give **E21** as a yellow powder (9.67 mg). The compound is the cis racemate at the pyrrolidine ring (mixture of 3aR,10aR and 3aS,10aS). ^{1}H NMR (300 MHz, DMSO-d6) δ ppm 1.11 (dd,

J=6.51, 2.11 Hz, 6 H) 2.78 - 2.90 (m, 1 H) 2.93 - 3.07 (m, 1 H) 3.07 - 3.18 (m, 1 H) 3.24 - 3.35 (m, 1 H) 3.41 (dt, J=12.95, 6.41 Hz, 1 H) 3.55 - 3.66 (m, 1 H) 3.80 (s, 3 H) 3.95 (t, J=11.28 Hz, 1 H) 4.46 - 4.60 (m, 2 H) 7.10 (br s, 1 H) 7.49 (s, 1 H) 7.62 - 7.72 (m, 2 H) 8.35 (d, J=10.00 Hz, 1 H) 9.63 (s, 1 H). Method 3: Rt= 3.62 min, m/z=552 $(M+H)^+$.

Example 22: cis-(3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-yl 7-methyl-8-((3,4,5-trifluorophenyl)carbamoyl)-3a,4,10,10a-tetrahydro-1H,7H-dipyrrolo[3,4-b:3',4'-f][1,4,5]oxathiazocine-2(3H)-carboxylate 5,5-dioxide (E22)

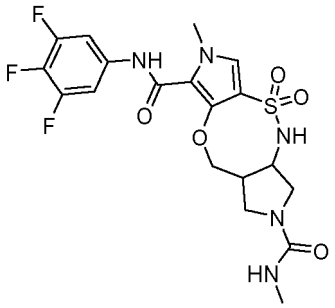
[0273]



[0274] To a suspension of **E11** (25 mg, 0.058 theoretical mmol) in dry DCM (0.5 mL), 2,5-dioxopyrrolidin-1-yl ((3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-yl) carbonate (15.8 mg, 0.058 mmol) and dry DIPEA (0.020mL, 0.115 mmol) were added at room temperature. After 1h conversion was completed. Crude was diluted with DCM and washed with 5% citric acid solution. Organic layer was dried over Na_2SO_4, filtered and evaporated. Residue was purified with preparative HPLC-MS (H_2O/CH_3CN +0.1% TFA) to give **E22** as a white powder (14.78 mg). The compound is the cis racemate at the pyrrolidine ring (racemate of 3aR,10aR and 3aS,10aS). ^{1}H NMR (300 MHz, DMSO-d_6+TFA) δ ppm 1.73 - 1.89 (m, 1 H) 1.89 - 2.06 (m, 1 H) 2.94 - 3.15 (m, 3 H) 3.37 - 3.49 (m, 2 H) 3.58 - 3.97 (m, 9 H) 4.40 - 4.51 (m, 1 H) 4.51 - 4.63 (m, 1 H) 5.00 - 5.08 (m, 1 H) 5.60 (t, *J*=4.31 Hz, 1 H) 7.50 (s, 1 H) 7.62 - 7.73 (m, 2 H) 8.41 - 8.49 (m, 1 H) 9.64 (s, 1 H). Method 3: Rt= 3.37 min, m/z=587 $(M+H)^+$.

Example 23: (3aR,10aR) and **(3aS,10aS) -*N*^{2},7-dimethyl-N^8-(3,4,5-trifluorophenyl)-3a,4,10,10a-tetrahydro-*1H*,*7H*-dipyrrolo[3,4-b:3',4'-*f*][1,4,5]oxathiazocine-2,8(*3H*)-dicarboxamide 5,5-dioxide (E23)**

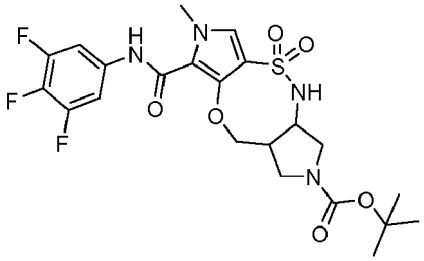
[0275]



[0276] To a suspension of **E11** (25 mg, 0.058 theoretical mmol), in dry acetonitrile (0.5 mL), N-methylcarbamoyl chloride (6.5 mg, 0.070 mmol) and dry DIPEA (0.025 mL, 0.058 mmol) were added at room temperature. Reaction was stopped after 2.5h when conversion was completed. Water (0.050 mL) was added and mixture evaporated under reduced pressure. Crude was purified with preparative HPLC-MS (H_2O/CH_3CN +0.1% TFA) to give **E23** as a pale yellow powder (13.26 mg). ^{1}H NMR (300 MHz, DMSO-d_6+TFA) δ ppm 2.58 (s, 3 H) 2.90 - 3.07 (m, 2 H) 3.28 - 3.46 (m, 2 H) 3.59 - 3.70 (m, 1 H) 3.80 (s, 3 H) 3.91 (br t, J=10.73 Hz, 1 H) 4.40 - 4.50 (m, 1 H) 4.53 - 4.64 (m, 1 H) 7.48 (s, 1 H) 7.61 - 7.74 (m, 2 H) 8.40 (d, J=10.00 Hz, 1 H) 9.63 (s, 1 H). Method 3: Rt= 3.04 min, m/z=488 $(M+H)^+$. The compound is the cis racemate at the pyrrolidine ring.

Example 24: tert-butyl (3aS,10aS and 3aR,10aR) 7-methyl-8-((3,4,5-trifluorophenyl)carbamoyl)-3a,4,10,10a-tetrahydro-1H,7H-dipyrrolo[3,4-b:3',4'-f][1,4,5]oxathiazocine-2(3H)-carboxylate 5,5-dioxide (E24)

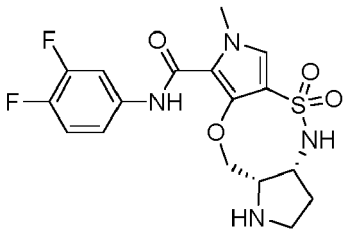
[0277]



[0278] Crude **D42** (61mg, 0.11mmol) was dissolved in DMF (2.8ml), cesium carbonate (90.4mg, 0.28mmol) was added and the reaction mixture was heated at 130°C under MW irradiation for 45min. Reaction mixture was diluted with EtOAc and washed with 5% citric acid solution and water. Organic layer was dried over Na_2SO_4, filtered and concentrated under vacuo. The resulting crude was purified by flash chromatography on silica (DCM/EtOAc) to obtain the title compound **E24** as a light brown powder (40mg, y=67%). ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 1.41 (s, 9 H) 2.82 - 3.11 (m, 2 H) 3.33 - 3.44 (m, 2 H) 3.62 - 3.76 (m, 1 H) 3.80 (s, 3 H) 3.84 - 3.97 (m, 1 H) 4.31 - 4.48 (m, 1 H) 4.49 - 4.71 (m, 1 H) 7.50 (s, 1 H) 7.61 - 7.81 (m, 2 H) 8.46 (br s, 1 H) 9.68 (s, 1 H) Method 3: Rt=3.87min. m/z=531.39 $(M+H)^+$. The compound is the cis racemate at the pyrrolidine ring.

Example 25: (3aR,10aS)-N-(3,4-difluorophenyl)-7-methyl-2,3,3a,4,10,10a-hexahydro-1H,7H-dipyrrolo[3,4-b:3',2'-f][1,4,5]oxathiazocine-8-carboxamide 5,5-dioxide (E25)

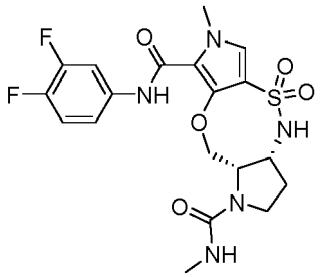
[0279]



[0280] In a 25mL microwave vial, crude **D44** (theoretical 0.261mmol, 139mg, 1eq) was dissolved in dry DMF (8.6mL, 0.030M), caesium carbonate (255mg, 0.783mmol, 3eq) was added, the vial was sealed and reaction mixture was heated at microwave at 130°C for a total of 4h10min in 5 runs. Reaction mixture was quenched in 5% aqueous citric acid solution, product was extracted with ethyl acetate, organic layer was washed once with 5% aqueous citric acid solution and once with brine, dried over sodium sulfate, filtered and solvent was removed under reduced pressure affording 114mg of brownish powder. Crude was purified with flash chromatography (DCM/AcOEt 7/3) to afford the Boc protected intermediate as a beige solid (71.2mg, y= 53%). Method 1: Rt=2.21 min, MH+ = 513 m/z. The compound from previous step (67mg, 0.131mmol, 1eq) was dissolved in DCM (2mL, 0.065M), triethylsilane (23uL, 0.144mol, 1.1eq) was added and trifluoroacetic acid (200uL, 2.612mmol, 20eq) was added and reaction mixture was stirred at rt. Complete conversion after 6h. Reaction mixture was diluted with DCM, brine was added, organic layer was removed, NaOH 20% was added to brine until pH=10 and product was extracted twice with ethyl acetate. Organic layers were combined, dried over sodium sulfate, filtered and solvent was removed under reduced pressure affording 54mg of crude product. 32mg were used without any purification, 19mg were purified with preparative HPLC-MS (H_2O,CH_3CN 0.1% TFA) to afford **E25** as a white powder (9.56mg). Method 3: Rt=2.21 min, MH+ = 413 m/z. Stereochemistry cis, single enantiomer. ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 1.97 - 2.10 (m, 1 H) 2.32 - 2.45 (m, 1 H) 3.27 - 3.46 (m, 2 H) 3.81 (s, 3 H) 3.92 - 4.05 (m, 1 H) 4.40 - 4.53 (m, 1 H) 4.53 - 4.68 (m, 2 H) 7.32 - 7.56 (m, 3 H) 7.83 (ddd, *J*=13.02, 7.34, 2.02 Hz, 1 H) 8.22 (d, J=7.50 Hz, 1 H) 8.61 - 8.83 (m, 1 H) 9.17 - 9.37 (m, 1 H) 9.58 (s, 1 H).

Example 26: (3aR,10aS)-N8-(3,4-difluorophenyl)-N1,7-dimethyl-2,3,3a,4,10,10a-hexahydro-1H,7H-dipyrrolo[3,4-b:3',2'-f][1,4,5]oxathiazocine-1,8-dicarboxamide 5,5-dioxide (E26)

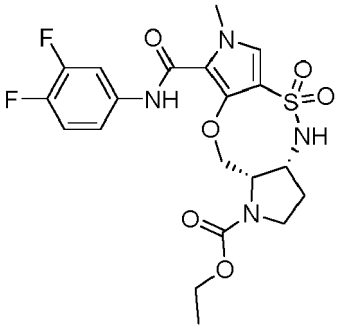
[0281]



[0282] Crude **E25** (16mg, 0.039mmol, 1eq) was dissolved in dry MeCN (1.6mL, 0.024M), N-methylcarbamoyl chloride (6.1mg, 0.065mmol, 1.68eq) was added, N,N-diisopropylethylamine (40uL, 0.230mmol, 5.9eq) was added and reaction mixture was stirred at rt. Complete conversion after 45min. Reaction mixture was concentrated under reduced pressure and crude product was purified with preparative HPLC-MS (H_2O,CH_3CN 0.1% TFA) to afford **E26** as a white yellow powder (6.98mg). Method 3: Rt=2.85 min, MH+ = 470 m/z. Stereochemistry cis, single enantiomer. ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 1.66 - 1.99 (m, 1 H) 2.01 - 2.26 (m, 1 H) 2.53 - 2.57 (m, 3 H) 3.16 - 3.40 (m, 2 H) 3.80 (s, 3 H) 4.04 - 4.35 (m, 3 H) 4.49 (br d, *J*=8.44 Hz, 1 H) 7.33 - 7.52 (m, 3 H) 7.87 (ddd, *J*=13.02, 7.52, 2.02 Hz, 1 H) 8.18 (br d, *J*=8.44 Hz, 1 H) 9.58 (s, 1 H).

Example 27: Ethyl (3aR,10aS)-8-((3,4-difluorophenyl)carbamoyl)-7-methyl-2,3,3a,4,10,10a-hexahydro-1H,7H-dipyrrolo[3,4-b:3',2'-f][1,4,5]oxathiazocine-1-carboxylate 5,5-dioxide (E27)

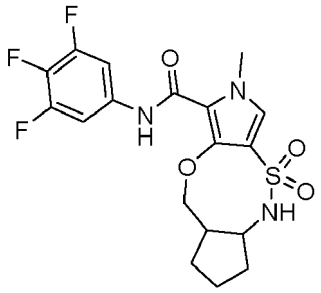
[0283]



[0284] Crude **E25** (16mg, 0.039mmol, 1eq) was dissolved in dry MeCN (1.6mL, 0.024M), ethyl chloroformate (5uL, 0.052mmol, 1.35eq) was added, N,N-diisopropylethylamine (40uL, 0.230mmol, 5.9eq) was added and reaction mixture was stirred at rt. Complete conversion after 50min. Reaction mixture was concentrated under reduced pressure and crude product was purified with preparative HPLC-MS (H_2O,CH_3CN 0.1% TFA) to afford **E27** as a light yellow powder (9.38mg). Method 3: Rt=3.42 min, MH+ = 485 m/z. ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 1.13 (br s, 3 H) 1.78 - 1.94 (m, 1 H) 2.05 - 2.25 (m, 1 H) 3.20 - 3.52 (m, 2 H) 3.81 (s, 3 H) 3.92 - 4.08 (m, 2 H) 4.08 - 4.62 (m, 4 H) 7.28 - 7.46 (m, 2 H) 7.50 (br s, 1 H) 7.71 - 7.97 (m, 1 H) 8.08 - 8.38 (m, 1 H) 9.62 (br s, 1 H).

Example 28: cis (5aR,8aS and 5aS,8aR)-2-methyl-N-(3,4,5-trifluorophenyl)-5a,6,7,8,8a,9-hexahydro-2H,5H-cyclopenta[f]pyrrolo[3,4-b][1,4,5]oxathiazocine-1-carboxamide 4,4-dioxide (E28)

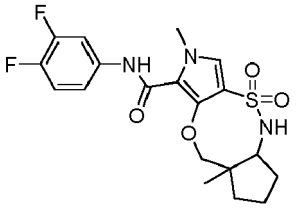
[0285]



[0286] In a microwave **D43** (66.9mg, 0.149mmol, 1eq) was dissolved in dry DMF (6mL), cesium carbonate (121.26mg, 0.327mmol, 2.5eq) was added, the vial sealed and mixture heated at microwave at 130°C for 30 min. The mixture was diluted with toluene, organic layer was washed with water, dried over Na_2SO_4, filtered and solvent was removed under reduced pressure. Crude product was purified on silica gel with flash chromatography affording 20mg of pure **E28.** ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 1.10 - 1.30 (m, 1 H) 1.42 - 1.76 (m, 4 H) 2.03 - 2.16 (m, 1 H) 2.53 - 2.62 (m, 1 H) 3.81 (s, 3 H) 3.86 (t, *J*=11.60 Hz, 1 H) 4.21 - 4.34 (m, 1 H) 4.50 (br dd, *J*=11.10, 4.31 Hz, 1 H) 7.47 (s, 1 H) 7.70 (dd, *J*=10.27, 6.42 Hz, 2 H) 7.89 (br d, *J*=9.90 Hz, 1 H) 9.63 (s, 1 H). Method 3: Rt= 3.84 min, m/z=430 $(M+H)^+$.

Example 29: N-(3,4-difluorophenyl)-2,8a-dimethyl-5a,6,7,8,8a,9-hexahydro-2H,5H-**cyclopenta[f]pyrrolo[3,4-b][1,4,5]oxathiazocine-1-carboxamide** 4,4-dioxide (E29)

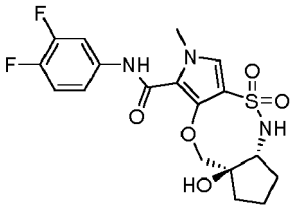
[0287]



[0288] Crude D45 (114mg, 0.193 theoretical mmol) was dissolved in dry DMF (4.8mL); Cs_2CO_3 (158mg, 0.482mmol, 2.5eq) was added and the mixture was heated to 130°C under MW irradiation for 1h: complete conversion. The reaction was diluted with EtOAc and washed with water and 5% citric acid (2x); the organic phase was dried over Na_2SO_4 and evaporated, yielding 100 mg of crude as an orange solid which was purified by preparative HPLC (H_2O,CH_3CN 0.1% TFA). Fractions containing product were freeze-dried, yielding 30.44 mg (y = 37%) of **E29** as a white powder. Method 3: Rt=3.72 min, MH+ = 426 m/z. ^{1}H NMR (300 MHz, DMSO-d6) δ ppm 0.83 (s, 3 H) 1.24 - 1.28 (m, 1 H) 1.42 - 1.60 (m. 4 H) 1.88 - 1.96 (m, 1 H) 3.75 - 3.78 (m, 1 H) 3.81 (s, 3 H) 3.89 - 3.92 (d, J=11.76 Hz, 1 H) 4.01 - 4.12 (d, J=11.76 Hz, 1 H) 7.37 - 7.49 (m, 3 H) 7.59 - 7.62 (d, J=9.81 Hz, 1 H) 7.84 - 7.91 (m, 1 H) 9.67 (s, 1H).

Example 30: cis-N-(3,4-difluorophenyl)-8a-hydroxy-2-methyl-5a,6,7,8,8a,9-hexahydro-2H,5H-cyclopenta[f]pyrrolo[3,4-b][1,4,5]oxathiazocine-1-carboxamide 4,4-dioxide (E30)

[0289]



[0290] Crude **D46** (38mg, 0.058 mmol) was dissolved in dry DMF (1.5mL); Cs_2CO_3 (47.2mg, 0.145mmol, 2.5eq) was added and the mixture was heated to 130°C under MW irradiation for 1h: complete conversion. The reaction was diluted with EtOAc and washed with water and 5% citric acid; the organic phase was dried over Na_2SO_4 and evaporated, yielding 47 mg of crude compound as a brown dense oil which was purified by preparative HPLC (H_2O,CH_3CN 0.1% HCOOH).

Fractions containing product were freeze-dried, yielding 3.92 mg (y = 15%) of **E30** as a pale pink powder. Method 3: Rt=3.33 min, MH+ = 428 m/z. Stereochemistry cis, racemic. ^{1}H NMR (300 MHz, DMSO-d6) δ ppm 1.42 - 1.72 (m, 2 H) 1.72 - 1.92 (m, 2 H) 1.97 - 2.17 (m. 1 H) 2.30 - 2.43 (m, 1 H) 3.45 (br d, J = 12.5 Hz, 1 H) 3.71 (br d, J = 12.0 Hz, 1 H) 3.81 (s, 3H) 3.95 - 4.13 (m, 1 H) 6.11 (br s, 1 H) 7.14 - 7.33 (m, 1 H) 7.34 - 7.58 (m ,2 H) 7.79 (dddd, J = 24.7, 13.1, 7.4, 2.5 Hz, 1 H) 7.96 - 8.14 (m, 1H) 10.05 - 10.27 (m, 1H).

[0291] The compounds shown in **Table 1** were obtained from Examples of the invention through the indicated preparative methods. In particular compounds **E31-E36** were obtained through Chiral HPLC Separation from the corresponding racemic mixtures, by Analytical Daicel Chiralpack IG Column, 0.46 cm I.D.x 25 cm L, Isocratic run at 50% Phase B (Phase A: H20 + 0.05% TFA and Phase B: Acetonitrile +0.05% TFA). The absolute stereochemistry is unknown, compounds are indicated as first eluted or second eluted enantiomer. Compound **E36** was obtained through deprotection by standard chemistry of compound **E33.**

Table 1:

Example	Compound Name	Preparative Method	Starting Material
E31	ethyl 7-methyl-8-((3,4,5-trifluorophenyl)carbamoyl)-3a, 4,10,10a-tetrahydro-1H,7H-dipyrrolo[3,4-b:3',4'-f][1,4,5] oxathiazocine-2(3H)-carboxylate 5,5-dioxide (Chiral 3aR,10aR or 3aS,10aS - Stereochemistry unknown)	Chiral Separation First eluted isomer	E10
E32	ethyl 7-methyl-8-((3,4,5-trifluorophenyl)carbamoyl)-3a, 4,10,10a-tetrahydro-1H,7H-dipyrrolo[3,4-b:3',4'-f][1,4,5] oxathiazocine-2(3H)-carboxylate 5,5-dioxide (Chiral 3aR,10aR or 3aS,10aS - Stereochemistry unknown)	Chiral Separation Second eluted isomer	E10
E33	tert-butyl 7-methyl-8-((3,4,5-trifluorophenyl)carbamoyl)-3a, 4,10,10a-tetrahydro-1H,7H-dipyrrolo[3,4-b:3',4'-f][1,4,5] oxathiazocine-2(3H)-carboxylate 5,5-dioxide (Chiral 3aS,10aS or 3aR,10aR - Stereochemistry unknown)	Chiral Separation First eluted isomer	E24
E34	N-(3,4-difluorophenyl)-2-methyl-5a,6,7,8,8a,9-hexahydro-2H, 5H-cyclopenta[f]pyrrolo[3,4-b][1,4,5]oxathiazocine-1-carboxamide 4,4-dioxide (Chiral 5aS,8aR or 5aR,8aS - Stereochemistry unknown)	Chiral Separation First eluted isomer	E6
E35	N-(3,4-difluorophenyl)-2-methyl-5a,6,7,8,8a,9-hexahydro-2H, 5H-cyclopenta[f]pyrrolo[3,4-b][1,4,5]oxathiazocine-1-carboxamide 4,4-dioxide (Chiral 5aS,8aR or 5aR,8aS - Stereochemistry unknown)	Chiral Separation Second eluted isomer	E6
E36	7-methyl-N-(3,4,5-trifluorophenyl)-2,3,3a,4,10,10a-hexahydro-1H,7H-dipyrrolo[3,4-b:3',4'-f][1,4,5]oxathiazocine-8-carboxamide 5,5-dioxide (Chiral 3aS,10aS or 3aR,10aR - Stereochemistry unknown)	Removal of the Boc protecting group	E33

Biology

Assay

Cells and culture conditions

[0292] HepAD38 cell line (Ladner et al., Antimicrob Agents Chemother, 1997, 41, 1715-20) was used for HBV inhibition assays. HepAD38 is a subclone, derived from Hepatoblastoma cell line HepG2 (ATCC® Number: HB-8065™), that expresses HBV genome under the control of a tetracycline-responsive promoter in a TET-OFF system: addition of tetracycline suppresses HBV replication, while its removal switches on the process allowing HBV viral particles release in the cell supernatant. HepAD38 cell line is maintained in DMEM/F12, supplemented with 10% of fetal bovine serum, 1% of glutamine, 1% of penicillin/streptomycin, 0.4 mg/ml G418 and 0,3 ug/ml tetracycline. For the HBV inhibition assay, doxycycline-free medium is used in order to allow virion production.

Anti-HBV activity *in vitro*

[0293] HBV inhibition activity in vitro was performed in 96 multiwell plates. During the initial (primary) screening compounds were first tested in triplicates at concentrations of 0.1μM, 0.5μM amd 1μM. For selected compounds, an 8-point dose-response curve can be obtained using 1:2 serial dilutions (starting from 2.5 μM, 1.25μM or 0.4 μM, depending on the degree of inhibition observed during the primary screening). From the dose-response curves, half maximal effective concentration (EC_{50}) can be calculated (see also below).

[0294] In more detail, compounds - typically dissolved in DMSO stock solutions - are diluted to 2x the final desired concentration in 100 μl of the above medium (without doxycycline) and plated in three replicates in the 96-well plates.

[0295] Simultaneously, HepAD38 cells - extensively pre-washed in tetracycline-free medium in order to induce HBV production - are suspended at $2*10^4$ cells in 100 μl of tetracycline-free medium and added to each well of the plate, to yield a final assay volume of 200 μl DMSO - used for stock solutions and compounds dilutions - which is always present in the assays at a final concentration of 0.5%.

[0296] Plates are then incubated 96 hours at 37°C and then subjected to cell viability assay in order to define compounds cytotoxicity and to extracellular HBV quantification in order to evaluate antiviral activity of compounds. Cytotoxicity is assessed by a commercial fluorescence assay that measures the metabolic activity of cells, directly related to cell viability (Cell Titer Blue, Promega). Anti-HBV activity was evaluated by quantification of extracellular HBV DNA with direct qPCR. In particular, supernatant was collected and centrifuged for cell debris clarification, viral DNA was extracted from virions by addition of lysis buffer (1 mM 1,4-dithiothreitol, 0.2% sodium dodecyl sulphate) and incubated at 95°C for 10 min. Samples were then diluted 1:40 and real time PCR amplification was performed with SYBR green assay (Power SYBR™ Green PCR Master Mix-Thermo Fisher Scientific) and specific HBV primer (HBV-DF:5'-ATTTGTTCAGTGGTTCGTAGGG-3' (SEQ ID No. 1), HBV-DR:5'-CGGTAAAAAGGGACTCAAGATG-3' (SEQ ID No. 2)).

[0297] All HBV inhibition or antiviral activity data are typically reported in percent (%) relative to a non-treated reference sample. Excel and Graphpad Prism programs are typically used for data elaboration and EC_{50} calculation.

RESULTS

[0298] The exemplified compounds described herein were tested in the assays described above. All the compounds displayed no measurable cytotoxicity at the tested compound concentration.

[0299] Results for HBV inhibition are reported in the following Table 2.

[0300] Legend: A indicates HBV inhibition greater than 50% at the concentration indicated in the table or EC_{50} less than 1μM; B indicates HBV inhibition less than 50% at the concentration indicated in the table or EC_{50} greater than 1μM.

Table 2

Example	**Compound Name**	**Anti HBV Activity (conc μM)**	**HBV inh EC_{50} (μM)**
E1	N-(3,4-difluorophenyl)-2-methyl-6,7,8,9,9a,10-hexahydro-2H-pyrido[1,2-e]pyrrolo[3,4-b][1,4,5]oxathiazepine-1-carboxamide 4,4-dioxide	B(1)	B
E2	N-(3,4-difluorophenyl)-2-methyl-2,6,7,8,9,9a,10,11-octahydropyrido[1,2-b]pyrrolo[3,4-f][1,2,5]thiadiazepine-1-carboxamide 4,4-dioxide	B(1)	-
E3	N-(3,4-difluorophenyl)-2-methyl-6,7,7a,8-tetrahydro-2H-azeto[1,2-e] pyrrolo[3,4-b][1,4,5]oxathiazepine-1-carboxamide 4,4-dioxide	A(1)	A
E4	*trans*-N-(3,4-difluorophenyl)-7-methyl-1,3a,4,9a-tetrahydro-3H,7H-furo [3,4-f]pyrrolo[3,4-b][1,4,5]oxathiazepine-8-carboxamide 5,5-dioxide	A(1)	A
E5	*cis*-N-(3,4-difluorophenyl)-9-methyl-3,4,5,6-tetrahydro-2H,9H-3,5-methanopyrrolo[3,4-b][1,4,5]oxathiazonine-8-carboxamide 1,1-dioxide	B(1)	-
E6	*cis*-N-(3,4-difluorophenyl)-2-methyl-5a,6,7,8,8a,9-hexahydro-2H,5H-cyclopenta[f]pyrrolo[3,4-b][1,4,5]oxathiazocine-1-carboxamide 4,4-dioxide	A (0,5)	A
E7	*trans*-7-methyl-N-(3,4,5-trifluorophenyl)-1,3a,4,9a-tetrahydro-3H,7H-furo[3,4-f]pyrrolo[3,4-b][1,4,5]oxathiazepine-8-carboxamide 5,5-dioxide	-	A

(continued)

Example	Compound Name	Anti HBV Activity (conc μM)	HBV inh EC_{50} (μM)
E8	(5aR,8aR)-N-(3,4-difluorophenyl)-2-methyl-5a,6,7,8,8a,9-hexahydro-2H,5H-cyclopenta[f]pyrrolo[3,4-b][1,4,5]oxathiazocine-1-carboxamide 4,4-dioxide	-	A
E9	(5aS,8aS)-N-(3,4-difluorophenyl)-2-methyl-5a,6,7,8,8a,9-hexahydro-2H,5H-cyclopenta[f]pyrrolo[3,4-b][1,4,5]oxathiazocine-1-carboxamide 4,4-dioxide	-	A
E10	*cis*-Ethyl 7-methyl-8-((3,4,5-trifluorophenyl)carbamoyl)-3a,4,10,10a-tetrahydro-1H,7H-dipyrrolo[3,4-b:3',4'-f][1,4,5]oxathiazocine-2(3H)-carboxylate 5,5-dioxide	A (0,5)	A
E11	*cis*-7 -methyl- N-(3,4,5-trifluorophenyl)-2,3,3a,4, 1 0, 1 0a-hexahydro-1H,7H-dipyrrolo[3,4-b:3',4'-f][1,4,5]oxathiazocine-8-carboxamide 5,5-dioxide	A (0,1)	A
E12	*cis*-2,7-dimethyl-N-(3,4,5-trifluorophenyl)-2,3,3a,4,10,10a-hexahydro-1H,7H-dipyrrolo[3,4-b:3',4'-f][1,4,5]oxathiazocine-8-carboxamide 5,5-dioxide	A (0,1)	A
E13	*cis*-Ethyl 8-((3,4-difluorophenyl)carbamoyl)-7-methyl-3a,4,10,10a-tetrahydro-1H,7H-dipyrrolo[3,4-b:3',4'-f][1,4,5]oxathiazocine-2(3H)-carboxylate 5,5-dioxide	A (0,1)	A
E14	*cis*-Ethyl 8-((4-fluoro-3-methylphenyl)carbamoyl)-7-methyl-3a,4,10,10a-tetrahydro-1H,7H-dipyrrolo[3,4-b:3',4'-f][1,4,5]oxathiazocine-2(3H)-carboxylate 5,5-dioxide	A (0,1)	A
E15	*cis*-Ethyl 8-((3-chloro-4-fluorophenyl)carbamoyl)-7-methyl-3a,4,10,10a-tetrahydro-1H,7H-dipyrrolo[3,4-b:3',4'-f][1,4,5]oxathiazocine-2(3H)-carboxylate 5,5-dioxide	A (0,1)	A
E16	*cis*-Ethyl 8-((3-(difluoromethyl)-4-fluorophenyl)carbamoyl)-7-methyl-3a,4,10,10a-tetrahydro-1H,7H-dipyrrolo[3,4-b:3',4'-f][1,4,5]oxathiazocine-2(3H)-carboxylate 5,5-dioxide	A (0,1)	A
E17	*cis*-Ethyl 8-((3-cyano-4-fluorophenyl)carbamoyl)-7-methyl-3a,4,10,10a-tetrahydro-1H,7H-dipyrrolo[3,4-b:3',4'-f][1,4,5]oxathiazocine-2(3H)-carboxylate 5,5-dioxide	A (0,1)	A
E18	*cis*-2-(isopropylsulfonyl)-7-methyl-N-(3,4,5-trifluorophenyl)-2,3,3a,4,10,10a-hexahydro-1 H,7H-dipyrrolo[3,4-b:3',4'-f] [1,4,5]oxathiazocine-8-carboxamide 5,5-dioxide	A (0,1)	A
E19	*cis*-7-methyl-2-(methylsulfonyl)-N-(3,4,5-trifluorophenyl)-2,3,3a,4,10,10a-hexahydro-1H,7H-dipyrrolo[3,4-b:3',4'-f][1,4,5]oxathiazocine-8-carboxamide 5,5-dioxide	A(0,1)	A
E20	*cis*-2-(cyclopropylsulfonyl)-7-methyl-N-(3,4,5-trifluorophenyl)-2,3,3a,4,10,10a-hexahydro-1 H,7H-dipyrrolo[3,4-b:3',4'-f] [1,4,5]oxathiazocine-8-carboxamide 5,5-dioxide	A (0,1)	A
E21	*cis*-2-(N-isopropylsulfamoyl)-7-methyl-N-(3,4,5-trifluorophenyl)-2,3,3a,4,10,10a-hexahydro-1H,7H-dipyrrolo[3,4-b:3',4'-f][1,4,5]oxathiazocine-8-carboxamide 5,5-dioxide	A (0,1)	A
E22	*cis*-(3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-yl 7-methyl-8-((3,4,5-trifluorophenyl)carbamoyl)-3a,4,10,10a-tetrahydro-1H,7H-dipyrrolo[3,4-b:3',4'-f][1,4,5]oxathiazocine-2(3H)-carboxylate 5,5-dioxide	A (0,1)	A

(continued)

Example	Compound Name	Anti HBV Activity (conc μM)	HBV inh EC_{50} (μM)
E23	N^2,7-dimethyl-N^8-(3,4,5-trifluorophenyl)-3a,4,10,10a-tetrahydro-1H,7H-dipyrrolo[3,4-b:3',4'-f][1,4,5]oxathiazocine-2,8(3H)-dicarboxamide 5,5-dioxide *(racemate of 3aR,10aR and 3aS,10aS)*	A (0,1)	A
E24	tert-butyl 7-methyl-8-((3,4,5-trifluorophenyl)carbamoyl)-3a,4,10,10a-tetrahydro-1H,7H-dipyrrolo[3,4-b:3',4'-f][1,4,5]oxathiazocine-2 (3H)-carboxylate 5,5-dioxide *(racemate of 3aS, 10aS and 3aR, 10aR)*	A (0,1)	-
E25	(3aR, 10aS)-N-(3,4-difluorophenyl)-7-methyl-2,3,3a,4,10,10a-hexahydro-1H,7H-dipyrrolo[3,4-b:3',2'-f][1,4,5]oxathiazocine-8-carboxamide 5,5-dioxide	B (0,1)	-
E26	(3aR,10aS)-N8-(3,4-difluorophenyl)-N1,7-dimethyl-2,3,3a,4,10,10a-hexahydro-1H,7H-dipyrrolo[3,4-b:3',2'-f][1,4,5]oxathiazocine-1,8-dicarboxamide 5,5-dioxide	B (0,1)	-
E27	ethyl (3aR,10aS)-8-((3,4-difluorophenyl)carbamoyl)-7-methyl-2,3,3a, 4,10,10a-hexahydro-1H,7H-dipyrrolo[3,4-b:3',2'-f][1,4,5]oxathiazocine-1-carboxylate 5,5-dioxide	B (0,1)	-
E28	*cis*-2-methyl-N-(3,4,5-trifluorophenyl)-5a,6,7,8,8a,9-hexahydro-2H,5H-cyclopenta[f]pyrrolo[3,4-b][1,4,5]oxathiazocine-1-carboxamide 4,4-dioxide	A (0,1)	A
E29	N-(3,4-difluorophenyl)-2,8a-dimethyl-5a,6,7,8,8a,9-hexahydro-2H,5H-cyclopenta[f]pyrrolo[3,4-b][1,4,5]oxathiazocine-1-carboxamide 4,4-dioxide	B (0,1)	-
E30	*cis*-N-(3,4-difluorophenyl)-8a-hydroxy-2-methyl-5a,6,7,8,8a,9-hexahydro-2H,5H-cyclopenta[f]pyrrolo[3,4-b][1,4,5]oxathiazocine-1-carboxamide 4,4-dioxide	B (0,5)	-
E31	ethyl 7-methyl-8-((3,4,5-trifluorophenyl)carbamoyl)-3a,4,10,10a-tetrahydro-1H,7H-dipyrrolo[3,4-b:3',4'-f][1,4,5]oxathiazocine-2 (3H)-carboxylate 5,5-dioxide (Chiral 3aR,10aR or 3aS,10aS - Stereochemistry unknown)	B (0,1)	-
E32	ethyl 7-methyl-8-((3,4,5-trifluorophenyl)carbamoyl)-3a,4,10,10a-tetrahydro-1H,7H-dipyrrolo[3,4-b:3',4'-f][1,4,5]oxathiazocine-2 (3H)-carboxylate 5,5-dioxide (Chiral 3aR,10aR or 3aS,10aS - Stereochemistry unknown)	A (0,1)	A
E33	tert-butyl 7-methyl-8-((3,4,5-trifluorophenyl)carbamoyl)-3a,4,10,10a-tetrahydro-1H,7H-dipyrrolo[3,4-b:3',4'-f][1,4,5]oxathiazocine-2 (3H)-carboxylate 5,5-dioxide (Chiral 3aS,10aS or 3aR,10aR - Stereochemistry unknown)	B (0,1)	-
E34	N-(3,4-difluorophenyl)-2-methyl-5a,6,7,8,8a,9-hexahydro-2H,5H-cyclopenta[f]pyrrolo[3,4-b][1,4,5] oxathiazocine-1 - carboxamide 4,4-dioxide (Chiral 5aS,8aR or 5aR,8aS - Stereochemistry unknown)	B (0,1)	-
E35	N-(3,4-difluorophenyl)-2-methyl-5a,6,7,8,8a,9-hexahydro-2H,5H-cyclopenta[f]pyrrolo[3,4-b][1,4,5] oxathiazocine-1 - carboxamide 4,4-dioxide (Chiral 5aS,8aR or 5aR,8aS - Stereochemistry unknown)	A (0,1)	A
E36	7-methyl-N-(3,4,5-trifluorophenyl)-2,3,3a,4,10,10a-hexahydro-1H,7H-dipyrrolo[3,4-b:3',4'-f][1,4,5]oxathiazocine-8-carboxamide 5,5-dioxide (Chiral 3aS,10aS or 3aR,10aR - Stereochemistry unknown)	B (0,1)	

SEQUENCE LISTING

<110> PROMIDIS S.R.L.
IRBM SCIENCE PARK S.P.A.
OSPEDALE SAN RAFFAELE S.R.L.
ISTITUTO NAZIONALE DI GENETICA MOLECOLARE – INGM

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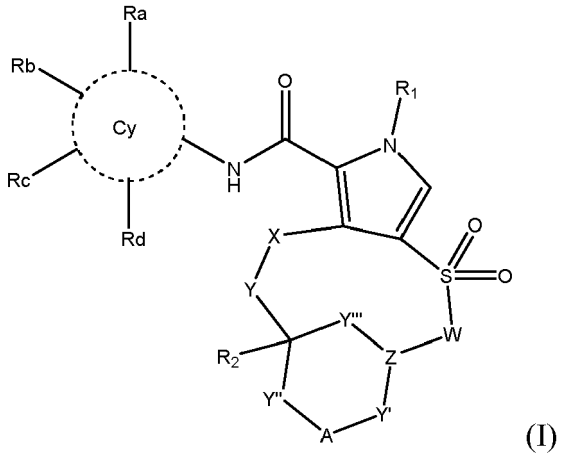
Claims

1. A compound of general formula (I):



(I)

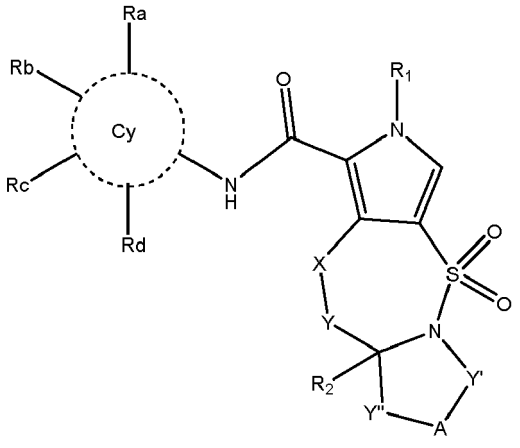
wherein:

Cy is aryl or heteroaryl;
X is O, NH or N-C_{1-6}alkyl;
Y, Y', Y" and Y'" are each independently a single bond or C_{1-6}alkanediyl optionally substituted with one or more R_3;
Z is CR_4 or N;
W is a single bond or NR_5, wherein if W is a single bond, Z is N, and if W is NR_5, Z is CR_4;
A is NR_6, O, S or C_{1-6}alkanediyl optionally substituted with one or more R_3;
R_1 is H or C_{1-6}alkyl;
R_2 is selected from H, OH and C_{1-6}alkyl;
R_3 is selected from H, OH, C_{1-6}alkyl, C_{3-8}cycloalkyl and halogen or two geminal R_3 form together with the atom to which they are attached a spiro-C_{3-8}cycloalkyl or a spiro-C_{3-8}heterocycloalkyl;
R_4 is H or C_{1-6}alkyl;
or when W is NR_5 and Z is CR_4, R_2 and R_4 may optionally form a C_{1-6}alkanediyl bridge;
R_5 is selected from H, C_{1-6}alkyl, C_{1-6}alkylaryl, C_{1-6}alkylheteroaryl and C_{1-6}alkyl-C_{3-8}cycloalkyl wherein each of said C_{1-6}alkyl, C_{1-6}alkylaryl, C_{1-6}alkylheteroaryl or C_{1-6}alkyl-C_{3-8}cycloalkyl is optionally substituted with one or more substituents each independently selected from: OH, halogen, haloC_{1-6}alkyl, cyano and NH_2;
R_6 is selected from:

- hydrogen;
- OH;
- $C(O)R_7$;
- $C(O)OR_7$;
- $C(O)NHR_7$;
- $C(O)N(R_7)_2$;
- SO_2R_7;
- $SO_2NH(R_7)$;
- $SO_2N(R_7)_2$;
- C_{1-6}alkyl optionally substituted with one or more substituents each independently selected from the group consisting of: OH, halogen, CN, NH_2, $NH(R_7)$, $N(R_7)_2$, aryl, heteroaryl, 3-7 membered saturated ring and 5-7 membered unsaturated ring, each of said saturated or unsaturated ring optionally containing one or more heteroatoms selected from the group consisting of O, N and S and each of said aryl, heteroaryl, 3-7 membered saturated or 5-7 membered unsaturated ring being optionally substituted with one or more substituents each independently selected from OH, halogen, haloC_{1-6}alkyl, CN, haloC_{1-6}alkoxy and C_{1-6}alkoxy;
- aryl or heteroaryl ring, each of said aryl or heteroaryl ring being optionally substituted with one or more substituents each independently selected from: OH, halogen, haloC_{1-6}alkyl, CN, haloC_{1-6}alkoxy and C_{1-6}alkoxy; and
- a 3-8 membered saturated or partially unsaturated cyclic or bicyclic ring optionally containing one or more heteroatoms each independently selected from the group consisting of: O, S and N, the 3-8 membered saturated or partially unsaturated cyclic or bicyclic ring being optionally substituted with one, two or more substituents each independently selected from the group consisting of: OH, halogen, CN, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, $C(O)OR_7$, $C(O)R_7$, haloC_{1-6}alkyl, haloC_{1-6}alkoxy and C_{1-6}alkoxy;

R_7 is selected from the group consisting of: C_{1-6}alkyl, C_{3-8}cycloalkyl, aryl, heteroaryl and 3-8 membered saturated or partially saturated heterocyclic ring, wherein each of said C_{1-6}alkyl, C_{3-}scycloalkyl, aryl, heteroaryl or 3-8 membered saturated or partially saturated heterocyclic ring is optionally substituted with one or more substituents each independently selected from the group consisting of: OH, halogen, CN, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, haloC_{1-6}alkyl, haloC_{1-6}alkoxy and
C_{1-6}alkoxy;
Ra, Rb, Rc and Rd are each idependently selected from the group consisting of: hydrogen, halogen, CN, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl and haloC_{1-6}alkoxy;
and pharmaceutically acceptable salts, tautomers, isomers, stereoisomers thereof.

2. The compound according to claim 1 having general formula (Ia):



(Ia)

wherein:

Cy is aryl or heteroaryl;
X is O, NH or N-C_{1-6}alkyl;
Y, Y' and Y" are each independently a single bond or C_{1-6}alkanediyl optionally substituted with one or more R_3;
A is NR_6, O, S or C_{1-6}alkanediyl optionally substituted with one or more R_3;
R_1 is H or C_{1-6}alkyl;
R_2 is selected from H, OH and C_{1-6}alkyl;
R_3 is selected from H, OH, C_{1-6}alkyl, C_{3-8}cycloalkyl and halogen or two geminal R_3 form together with the atom to which they are attached a spiro-C_{3-8}cycloalkyl or a spiro-C_{3-8}heterocycloalkyl;
R_5 is selected from:

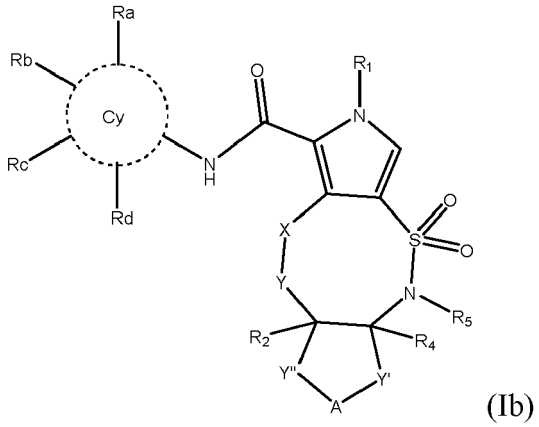
- hydrogen;
- OH;
- $C(O)R_7$;
- $C(O)OR_7$;
- $C(O)NHR_7$;
- $C(O)N(R_7)_2$;
- SO_2R_7;
- $SO_2NH(R_7)$;
- $SO_2N(R_7)_2$;
- C_{1-6}alkyl optionally substituted with one or more substituents each independently selected from the group consisting of: OH, halogen, CN, NH_2, $NH(R_7)$, $N(R_7)_2$, aryl, heteroaryl, 3-7 membered saturated ring and 5-7 membered unsaturated ring, each of said saturated or unsaturated ring optionally containing one or more heteroatoms selected from the group consisting of O, N and S and each of said aryl, heteroaryl, 3-7 membered saturated or 5-7 membered unsaturated ring being optionally substituted with one or more substituents each independently selected from OH, halogen, haloC_{1-6}alkyl, CN, haloC_{1-6}alkoxy and C_{1-6}alkoxy;
- aryl or heteroaryl ring, each of said aryl or heteroaryl ring being optionally substituted with one or more substituents each independently selected from: OH, halogen, haloC_{1-6}alkyl, CN, haloC_{1-6}alkoxy and C_{1-6}alkoxy; and
- a 3-8 membered saturated or partially unsaturated cyclic or bicyclic ring optionally containing one or more heteroatoms each independently selected from the group consisting of: O, S and N, the 3-8 membered saturated or partially unsaturated cyclic or bicyclic ring being optionally substituted with one, two or more substituents each independently selected from the group consisting of: OH, halogen, CN, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, $C(O)OR_7$, $C(O)R_7$, haloC_{1-6}alkyl, haloC_{1-6}alkoxy and C_{1-6}alkoxy;

R_7 is selected from the group consisting of: C_{1-6}alkyl, C_{3-8}cycloalkyl, aryl, heteroaryl and 3-8 membered saturated or partially saturated heterocyclic ring, wherein each of said C_{1-6}alkyl, C_{3-}scycloalkyl, aryl, heteroaryl or 3-8 membered saturated or partially saturated heterocyclic ring is optionally substituted with one or more substituents each independently selected from the group consisting of: OH, halogen, CN, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, haloC_{1-6}alkyl, haloC_{1-6}alkoxy and

C_{1-6}alkoxy;
Ra, Rb, Rc and Rd are each idependently selected from the group consisting of: hydrogen, halogen, CN, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl and haloC_{1-6}alkoxy;
and pharmaceutically acceptable salts, tautomers, isomers, stereoisomers thereof.

3. The compound according to claim 2, wherein: Cy is phenyl, X is O or NH, A is CH_2, R_1 is CH_3, R_2 and R_3 are hydrogen, and pharmaceutically acceptable salts, tautomers, isomers, stereoisomers thereof.

4. The compound according to claim 1 having the general formula (Ib):



(Ib)

wherein:

Cy is aryl or heteroaryl;
X is O, NH or N-C_{1-6}alkyl;
Y, Y' and Y" are each independently a single bond or C_{1-6}alkanediyl optionally substituted with one or more R_3;
A is NR_6, O, S or C_{1-6}alkanediyl optionally substituted with one or more R_3;
R_1 is H or C_{1-6}alkyl;
R_2 is selected from H, OH and C_{1-6}alkyl;
R_3 is selected from H, OH, C_{1-6}alkyl, C_{3-8}cycloalkyl and halogen or two geminal R_3 form together with the atom to which they are attached a spiro-C_{3-8}cycloalkyl or a spiro-C_{3-8}heterocycloalkyl;
R_4 is H or C_{1-6}alkyl;
or R_2 and R_4 may optionally form a C_{1-6}alkanediyl bridge;
R_5 is selected from H, C_{1-6}alkyl, C_{1-6}alkylaryl, C_{1-6}alkylheteroaryl and C_{1-6}alkyl-C_{3-8}cycloalkyl wherein each of said C_{1-6}alkyl, C_{1-6}alkylaryl, C_{1-6}alkylheteroaryl or C_{1-6}alkyl-C_{3-8}cycloalkyl is optionally substituted with one or more substituents each independently selected from: OH, halogen, haloC_{1-6}alkyl, cyano and NH_2;
R_6 is selected from:

- hydrogen;
- OH;
- $C(O)R_7$;
- $C(O)OR_7$;
- $C(O)NHR_7$;
- $C(O)N(R_7)_2$;
- SO_2R_7;
- $SO_2NH(R_7)$;
- $SO_2N(R_7)_2$;
- C_{1-6}alkyl optionally substituted with one or more substituents each independently selected from the group consisting of: OH, halogen, CN, NH_2, $NH(R_7)$, $N(R_7)_2$, aryl, heteroaryl, 3-7 membered saturated ring and 5-7 membered unsaturated ring, each of said saturated or unsaturated ring optionally containing one or more heteroatoms selected from the group consisting of O, N and S and each of said aryl, heteroaryl, 3-7 membered saturated or 5-7 membered unsaturated ring being optionally substituted with one or more substituents each independently selected from OH, halogen, haloC_{1-6}alkyl, CN, haloC_{1-6}alkoxy and C_{1-6}alkoxy;

- aryl or heteroaryl ring, each of said aryl or heteroaryl ring being optionally substituted with one or more substituents each independently selected from: OH, halogen, haloC_{1-6}alkyl, CN, haloC_{1-6}alkoxy and C_{1-6}alkoxy; and
- a 3-8 membered saturated or partially unsaturated cyclic or bicyclic ring optionally containing one or more heteroatoms each independently selected from the group consisting of: O, S and N, the 3-8 membered saturated or partially unsaturated cyclic or bicyclic ring being optionally substituted with one, two or more substituents each independently selected from the group consisting of: OH, halogen, CN, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, C(O)OR_7, C(O)R_7, haloC_{1-6}alkyl, haloC_{1-6}alkoxy and C_{1-6}alkoxy;

R_7 is selected from the group consisting of: C_{1-6}alkyl, C_{3-8}cycloalkyl, aryl, heteroaryl and 3-8 membered saturated or partially saturated heterocyclic ring, wherein each of said C_{1-6}alkyl, C_{3-8}cycloalkyl, aryl, heteroaryl or 3-8 membered saturated or partially saturated heterocyclic ring is optionally substituted with one or more substituents each independently selected from the group consisting of: OH, halogen, CN, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, haloC_{1-6}alkyl, haloC_{1-6}alkoxy and C_{1-6}alkoxy;

Ra, Rb, Rc and Rd are each idependently selected from the group consisting of: hydrogen, halogen, CN, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl and haloC_{1-6}alkoxy;

and pharmaceutically acceptable salts, tautomers, isomers, stereoisomers thereof.

5. The compound according to claim 4 wherein: Cy is phenyl, X is O, Y is CH_2, Y' is CH_2, Y" is CH_2 and A is CH_2, O or NR_6, and pharmaceutically acceptable salts, tautomers, isomers, stereoisomers thereof

6. The compound of general formula (I) according to claim 1 being selected from the following list:

- N-(3,4-difluorophenyl)-2-methyl-6,7,8,9,9a,10-hexahydro-2H-pyrido[1,2-e]pyrrolo[3,4-b][1,4,5]oxathiazepine-1-carboxamide 4,4-dioxide;
- N-(3,4-difluorophenyl)-2-methyl-2,6,7,8,9,9a,10,11-octahydropyrido[1,2-b]pyrrolo[3,4-f]1,2,5]thiadiazepine-1-carboxamide 4,4-dioxide;
- N-(3,4-difluorophenyl)-2-methyl-6,7,7a,8-tetrahydro-2H-azeto[1,2-e]pyrrolo[3,4-b][1,4,5]oxathiazepine-1-carboxamide 4,4-dioxide;
- *trans*-N-(3,4-difluorophenyl)-7-methyl-1,3a,4,9a-tetrahydro-3H,7H-furo[3,4-f]pyrrolo[3,4-b][1,4,5]oxathiazepine-8-carboxamide 5,5-dioxide;
- *cis*-N-(3,4-difluorophenyl)-9-methyl-3,4,5,6-tetrahydro-2H,9H-3,5-methanopyrrolo[3,4-b][1,4,5]oxathiazonine-8-carboxamide 1,1-dioxide;
- *cis*-N-(3,4-difluorophenyl)-2-methyl-5a,6,7,8,8a,9-hexahydro-2H,5H-cyclopenta[f]pyrrolo[3,4-b][1,4,5]oxathiazocine-1-carboxamide 4,4-dioxide;
- *trans*-7-methyl-N-(3,4,5-trifluorophenyl)-1,3a,4,9a-tetrahydro-3H,7H-furo[3,4-f]pyrrolo[3,4-b][1,4,5]oxathiazepine-8-carboxamide 5,5-dioxide;
- (5aR,8aR)-N-(3,4-difluorophenyl)-2-methyl-5a,6,7,8,8a,9-hexahydro-2H,5H-cyclopenta[f]pyrrolo[3,4-b][1,4,5]oxathiazocine-1-carboxamide 4,4-dioxide;
- (5aS,8aS)-N-(3,4-difluorophenyl)-2-methyl-5a,6,7,8,8a,9-hexahydro-2H,5H-cyclopenta[f]pyrrolo[3,4-b][1,4,5]oxathiazocine-1-carboxamide 4,4-dioxide;
- *cis*-Ethyl 7-methyl-8-((3,4,5-trifluorophenyl)carbamoyl)-3a,4,10,10a-tetrahydro-1H,7H-dipyrrolo[3,4-b:3',4'-f][1,4,5]oxathiazocine-2(3H)-carboxylate 5,5-dioxide;
- *cis*-7-methyl-N-(3,4,5-trifluorophenyl)-2,3,3a,4,10,10a-hexahydro-1H,7H-dipyrrolo[3,4-b:3',4'-f][1,4,5]oxathiazocine-8-carboxamide 5,5-dioxide;
- *cis*-2,7-dimethyl-N-(3,4,5-trifluorophenyl)-2,3,3a,4,10,10a-hexahydro-1H,7H-dipyrrolo[3,4-b:3',4'-f][1,4,5]oxathiazocine-8-carboxamide 5,5-dioxide;
- *cis*-Ethyl 8-((3,4-difluorophenyl)carbamoyl)-7-methyl-3a,4,10,10a-tetrahydro-1H,7H-dipyrrolo[3,4-b:3',4'-f][1,4,5]oxathiazocine-2(3H)-carboxylate 5,5-dioxide;
- *cis*-Ethyl 8-((4-fluoro-3-methylphenyl)carbamoyl)-7-methyl-3a,4,10,10a-tetrahydro-1H,7H-dipyrrolo[3,4-b:3',4'-f][1,4,5]oxathiazocine-2(3H)-carboxylate 5,5-dioxide;
- *cis*-Ethyl 8-((3-chloro-4-fluorophenyl)carbamoyl)-7-methyl-3a,4,10,10a-tetrahydro-1H,7H-dipyrrolo[3,4-b:3',4'-f][1,4,5]oxathiazocine-2(3H)-carboxylate 5,5-dioxide;
- *cis*-Ethyl 8-((3-(difluoromethyl)-4-fluorophenyl)carbamoyl)-7-methyl-3a,4,10,10a-tetrahydro-1H,7H-dipyrrolo[3,4-b:3',4'-f][1,4,5]oxathiazocine-2(3H)-carboxylate 5,5-dioxide;
- *cis*-Ethyl 8-((3-cyano-4-fluorophenyl)carbamoyl)-7-methyl-3a,4,10,10a-tetrahydro-1H,7H-dipyrrolo[3,4-b:3',4'-f][1,4,5]oxathiazocine-2(3H)-carboxylate 5,5-dioxide;

- *cis*-2-(isopropylsulfonyl)-7-methyl-N-(3,4,5-trifluorophenyl)-2,3,3a,4,10,10a-hexahydro-1H,7H-dipyrrolo[3,4-b:3',4'-f][1,4,5]oxathiazocine-8-carboxamide 5,5-dioxide;
- *cis*-7-methyl-2-(methylsulfonyl)-N-(3,4,5-trifluorophenyl)-2,3,3a,4,10,10a-hexahydro-1H,7H-dipyrrolo[3,4-b:3',4'-f][1,4,5]oxathiazocine-8-carboxamide 5,5-dioxide;
- *cis*-2-(cyclopropylsulfonyl)-7-methyl-N-(3,4,5-trifluorophenyl)-2,3,3a,4,10,10a-hexahydro-1H,7H-dipyrrolo[3,4-b:3',4'-f][1,4,5]oxathiazocine-8-carboxamide 5,5-dioxide;
- *cis*-2-(N-isopropylsulfamoyl)-7-methyl-N-(3,4,5-trifluorophenyl)-2,3,3a,4,10,10a-hexahydro-1H,7H-dipyrrolo[3,4-b:3',4'-f][1,4,5]oxathiazocine-8-carboxamide 5,5-dioxide;
- cis-(3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-yl 7-methyl-8-((3,4,5-trifluorophenyl)carbamoyl)-3a,4,10,10a-tetrahydro-1H,7H-dipyrrolo[3,4-b:3',4'-f][1,4,5]oxathiazocine-2(3H)-carboxylate 5,5-dioxide;
- N^2,7-dimethyl-N^8-(3,4,5-trifluorophenyl)-3a,4,10,10a-tetrahydro-1H,7H-dipyrrolo[3,4-b:3',4'-f][1,4,5]oxathiazocine-2,8(3H)-dicarboxamide 5,5-dioxide;
- tert-butyl 7-methyl-8-((3,4,5-trifluorophenyl)carbamoyl)-3a,4,10,10a-tetrahydro-1H,7H-dipyrrolo[3,4-b:3',4'-f][1,4,5]oxathiazocine-2(3H)-carboxylate 5,5-dioxide;
- (3aR,10aS)-N-(3,4-difluorophenyl)-7-methyl-2,3,3a,4,10,10a-hexahydro-1H,7H-dipyrrolo[3,4-b:3',2'-f][1,4,5]oxathiazocine-8-carboxamide 5,5-dioxide;
- (3aR,10aS)-N8-(3,4-difluorophenyl)-N1,7-dimethyl-2,3,3a,4,10,10a-hexahydro-1H,7H-dipyrrolo[3,4-b:3',2'-f][1,4,5]oxathiazocine-1,8-dicarboxamide 5,5-dioxide;
- ethyl (3aR,10aS)-8-((3,4-difluorophenyl)carbamoyl)-7-methyl-2,3,3a,4,10,10a-hexahydro-1H,7H-dipyrrolo[3,4-b:3',2'-f][1,4,5]oxathiazocine-1-carboxylate 5,5-dioxide;
- *cis*-2-methyl-N-(3,4,5-trifluorophenyl)-5a,6,7,8,8a,9-hexahydro-2H,5H-cyclopenta[f]pyrrolo[3,4-b][1,4,5]oxathiazocine-1-carboxamide 4,4-dioxide;
- N-(3,4-difluorophenyl)-2,8a-dimethyl-5a,6,7,8,8a,9-hexahydro-2H,5H-cyclopenta[f]pyrrolo[3,4-b][1,4,5]oxathiazocine-1-carboxamide 4,4-dioxide;
- *cis*-N-(3,4-difluorophenyl)-8a-hydroxy-2-methyl-5a,6,7,8,8a,9-hexahydro-2H,5H-cyclopenta[f]pyrrolo[3,4-b][1,4,5]oxathiazocine-1-carboxamide 4,4-dioxide;
- (3aS,10aS)-7-methyl-N-(3,4,5-trifluorophenyl)-2,3,3a,4,10,10a-hexahydro-1H,7H-dipyrrolo[3,4-b:3',4'-f][1,4,5]oxathiazocine-8-carboxamide 5,5-dioxide;
- (3aR,10aR)-7-methyl-N-(3,4,5-trifluorophenyl)-2,3,3a,4,10,10a-hexahydro-1H,7H-dipyrrolo[3,4-b:3',4'-f][1,4,5]oxathiazocine-8-carboxamide 5,5-dioxide;
- ethyl (3aR,10aR)-7-methyl-8-((3,4,5-trifluorophenyl)carbamoyl)-3a,4,10,10a-tetrahydro-1H,7H-dipyrrolo[3,4-b:3',4'-f][1,4,5]oxathiazocine-2(3H)-carboxylate 5,5-dioxide;
- ethyl (3aS,10aS)-7-methyl-8-((3,4,5-trifluorophenyl)carbamoyl)-3a,4,10,10a-tetrahydro-1H,7H-dipyrrolo[3,4-b:3',4'-f][1,4,5]oxathiazocine-2(3H)-carboxylate 5,5-dioxide;
- tert-butyl (3aS,10aS)-7-methyl-8-((3,4,5-trifluorophenyl)carbamoyl)-3a,4,10,10a-tetrahydro-1H,7H-dipyrrolo[3,4-b:3',4'-f][1,4,5]oxathiazocine-2(3H)-carboxylate 5,5-dioxide;
- tert-butyl (3aR,10aR)-7-methyl-8-((3,4,5-trifluorophenyl)carbamoyl)-3a,4,10,10a-tetrahydro-1H,7H-dipyrrolo[3,4-b:3',4'-f][1,4,5]oxathiazocine-2(3H)-carboxylate 5,5-dioxide;
- (5aS,8aR) N-(3,4-difluorophenyl)-2-methyl-5a,6,7,8,8a,9-hexahydro-2H,5H-cyclopenta[f]pyrrolo[3,4-b][1,4,5]oxathiazocine-1-carboxamide 4,4-dioxide;
- (5aR,8aS) N-(3,4-difluorophenyl)-2-methyl-5a,6,7,8,8a,9-hexahydro-2H,5H-cyclopenta[f]pyrrolo[3,4-b][1,4,5]oxathiazocine-1-carboxamide 4,4-dioxide;

and pharmaceutically acceptable salts, tautomers, isomers, stereoisomers thereof.

7. A compound as defined in any one of previous claims for medical use.

8. The compound as defined in claim 7 for use in the treatment and/or prevention of a HBV infection.

9. The compound according to claim 8 for use in treating, eradicating, reducing, slowing or inhibiting an HBV infection in an individual in need thereof, and/or in reducing the viral load associated with an HBV infection in an individual in need thereof, and/or reducing reoccurrence of an HBV infection in an individual in need thereof, and/or inducing remission of hepatic injury from an HBV infection in an individual in need thereof, and/or prophylactically treating an HBV infection in an individual afflicted with a latent HBV infection.

10. The compound for use according to any one of claims 7-9, for use in combination with at least one further therapeutic agent.

11. The compound for use according to claim 10, wherein the at least one further therapeutic agent is selected from the group consisting of: a therapeutic vaccine; an RNA interference therapeutic/antisense oligonucleotide; an immunomodulator; a STING agonist; a RIG-I modulator; a NKT modulator; an IL agonist; an interleukin or another immune acting protein; a therapeutic and prophylactic vaccine; an immune checkpoint modulator/inhibitor; an HBV entry inhibitor; a cccDNA modulator; an inhibitor of HBV protein espression; an agent targeting HBV RNA; a capsid assembly inhibitor/modulator; a core or X protein targeting agent; a nucleotide analogue; a nucleoside analogue; an interferon or a modified interferon; an HBV antiviral of distinct or unknown mechanism; a cyclophilin inhibitor; a sAg release inhibitor; a HBV polymerase inhibitor; a dinucleotide; a SMAC inhibitor; a HDV targeting agent; a viral maturation inhibitor; a reverse transcriptase inhibitor and an HBV RNA destabilizer or another small-molecule inhibitor of HBV protein expression; or a combination thereof; wherein said therapeutic vaccine is preferably selected from: HBsAG-HBIG, HB-Vac, ABX203, NASVAC, GS-4774, GX-110 (HB-110E), CVI-HBV-002, RG7944 (INO-1800), TG-1050, FP-02 (Hepsyn-B), AIC649, VGX-6200, KW-2, TomegaVax-HBV, ISA-204, NU-500, INX-102-00557, HBV MVA and PepTcell; wherein said RNA interference therapeutic is preferably selected from: TKM-HBV (ARB-1467), ARB-1740, ARC-520, ARC-521, BB-HB-331, REP-2139, ALN-HBV, ALN-PDL, LUNAR-HBV, GS3228836 and GS3389404; wherein said immunomodulator is preferably a TLR agonist, preferably a TLR7, TLR8 or TLR9 agonist, preferably being selected from: RG7795 (RO-6864018), GS-9620, SM360320 (9-benzyl-8-hydroxy-2-(2-methoxyethoxy)adenine), AZD 8848 (methyl [3-({[3-(6-amino-2-butoxy-8-oxo-7,8-dihydro-9H-pyrin-9-yl)propyl][3-(4-morpholinyl)propyl]amino}methyl)phenyl]acetate) and ARB-1598; wherein said RIG-I modulator is preferably SB-9200; wherein said IL agonist or other immune acting protein is preferably INO-9112 or recombinant IL12; wherein said immune checkpoint modulator/inhibitor is preferably BMS-936558 (Opdivo (nivolumab)) or pembrolizumab; wherein said HBV entry inhibitor is preferably Myrcludex B, IVIG-Tonrol or GC-1102; wherein said cccDNA modulator is preferably selected from: a direct cccDNA inhibitor, an inhibitor of cccDNA formation or maintenance, a cccDNA epigenetic modifier and an inhibitor of cccDNA transcription; wherein said capsid assembly inhibitor/modulator, core or X protein targeting agent, direct cccDNA inhibitor, inhibitor of cccDNA formation or maintenance, or cccDNA epigenetic modifier is preferably selected from: BAY 41-4109, NVR 3-778, GLS-4, NZ-4 (W28F), Y101, ARB-423, ARB-199, ARB-596, AB-506, JNJ-56136379, ASMB-101 (AB-V102), ASMB-103, CHR-101, CC-31326, AT-130 and RO7049389; wherein said interferon or modified interferon is preferably selected from: interferon alpha (IFN-α), pegylated interferon alpha (PEG-IFN-α), interferon alpha-2a, recombinant interferon alpha-2a, peginterferon alpha-2a (Pegasys), interferon alpha-2b (Intron A), recombinant interferon alpha-2b, interferon alpha-2b XL, peginterferon alpha-2b, glycosylated interferon alpha-2b, interferon alpha-2c, recombinant interferon alpha-2c, interferon beta, interferon beta-la, peginterferon beta-la, interferon delta, interferon lambda (IFN-λ), peginterferon lambda-1, interferon omega, interferon tau, interferon gamma (IFN-γ), interferon alfacon-1, interferon alpha-nl, interferon alpha-n3, albinterferon alpha-2b, BLX-883, DA-3021, PI 101 (also known as AOP2014), PEG-infergen, Belerofon, INTEFEN-IFN, albumin/interferon alpha 2a fusion protein, rHSA-IFN alpha 2a, rHSA-IFN alpha 2b, PEG-IFN-SA and interferon alpha biobetter; wherein said HBV antiviral of distinct or unknown mechanism is selected from: AT-61 ((E)-N-(1-chloro-3-oxo-1-phenyl-3-(piperidin-1-yl)prop-1-en-2-yl)benzamide), AT130 ((E)-N-(1-bromo-1-(2-methoxyphenyl)-3-oxo-3-(piperidin-1-yl)prop-1-en-2-yl)-4-nitrobenzamide), analogues thereof, REP-9AC (REP-2055), REP-9AC' (REP-2139), REP-2165 and HBV-0259; wherein said cyclophilin inhibitor is preferably selected from: OCB-030 (NVP-018), SCY-635, SCY-575 and CPI-431-32; wherein said HBV polymerase inhibitor is preferably selected from: entecavir (Baraclude, Entavir), lamivudine (3TC, Zeffix, Heptovir, Epivir, and Epivir-HBV), telbivudine (Tyzeka, Sebivo), clevudine, besifovir, adefovir (hepsera), tenofovir, preferably said tenofovir is in a salt form selected from: tenofovir disoproxil fumarate (Viread), tenofovir alafenamide fumarate (TAF), tenofovir disoproxil orotate (DA-2802), tenofovir disopropxil aspartate (CKD-390), AGX-1009, and CMX157; wherein said dinucleotide is preferably SB9200; wherein said SMAC inhibitor is preferably Birinapant; wherein said HDV targeting agent is preferably Lonafamib; wherein said HBV RNA destabilizer or other small-molecule inhibitor of HBV protein expression is preferably RG7834 or AB-452.

12. A pharmaceutical composition comprising a compound as defined in anyone of claims 1-6, alone or in combination with at least one further therapeutic agent, and at least one pharmaceutically acceptable excipient.

13. The pharmaceutical composition according to claim 12, wherein the at least one further therapeutic agent is selected from the group consisting of: a therapeutic vaccine; an RNA interference therapeutic/antisense oligonucleotide; an immunomodulator; a STING agonist; a RIG-I modulator; a NKT modulator; an IL agonist; an interleukin or another immune acting protein; a therapeutic and prophylactic vaccine; an immune checkpoint modulator/inhibitor; an HBV entry inhibitor; a cccDNA modulator; an inhibitor of HBV protein espression; an agent targeting HBV RNA; a capsid assembly inhibitor/modulator; a core or X protein targeting agent; a nucleotide analogue; a nucleoside analogue; an interferon or a modified interferon; an HBV antiviral of distinct or unknown mechanism; a cyclophilin inhibitor; a sAg release inhibitor; a HBV polymerase inhibitor; a dinucleotide; a SMAC inhibitor; a HDV targeting agent; a viral

maturation inhibitor; a reverse transcriptase inhibitor and an HBV RNA destabilizer or another small-molecule inhibitor of HBV protein expression; or a combination thereof; wherein said therapeutic vaccine is preferably selected from: HBsAG-HBIG, HB-Vac, ABX203, NASVAC, GS-4774, GX- 110 (HB-110E), CVI-HBV-002, RG7944 (INO-1800), TG-1050, FP-02 (Hepsyn-B), AIC649, VGX-6200, KW-2, TomegaVax-HBV, ISA-204, NU-500, INX-102-00557, HBV MVA and PepTcell; wherein said RNA interference therapeutic is preferably selected from: TKM-HBV (ARB-1467), ARB-1740, ARC-520, ARC-521, BB-HB-331, REP-2139, ALN-HBV, ALN-PDL, LUNAR-HBV, GS3228836 and GS3389404; wherein said immunomodulator is preferably a TLR agonist, preferably a TLR7, TLR8 or TLR9 agonist, preferably being selected from: RG7795 (RO-6864018), GS-9620, SM360320 (9-benzyl-8-hydroxy-2-(2-methoxyethoxy)adenine), AZD 8848 (methyl [3-({[3-(6-amino-2-butoxy-8-oxo-7,8-dihydro-9H-pyrin-9-yl)propyl][3-(4-morpholinyl)propyl]amino}methyl)phenyl]acetate) and ARB-1598; wherein said RIG-I modulator is preferably SB-9200; wherein said IL agonist or other immune acting protein is preferably INO-9112 or recombinant IL12; wherein said immune checkpoint modulator/inhibitor is preferably BMS-936558 (Opdivo (nivolumab)) or pembrolizumab; wherein said HBV entry inhibitor is preferably Myrcludex B, IVIG-Tonrol or GC-1102; wherein said cccDNA modulator is preferably selected from: a direct cccDNA inhibitor, an inhibitor of cccDNA formation or maintenance, a cccDNA epigenetic modifier and an inhibitor of cccDNA transcription; wherein said capsid assembly inhibitor/modulator, core or X protein targeting agent, direct cccDNA inhibitor, inhibitor of cccDNA formation or maintenance, or cccDNA epigenetic modifier is preferably selected from: BAY 41-4109, NVR 3-778, GLS-4, NZ-4 (W28F), Y101, ARB-423, ARB-199, ARB-596, AB-506, JNJ-56136379, ASMB-101 (AB-V102), ASMB-103, CHR-101, CC-31326, AT-130 and RO7049389; wherein said interferon or modified interferon is preferably selected from: interferon alpha (IFN-α), pegylated interferon alpha (PEG-IFN-α), interferon alpha-2a, recombinant interferon alpha-2a, peginterferon alpha-2a (Pegasys), interferon alpha-2b (Intron A), recombinant interferon alpha-2b, interferon alpha-2b XL, peginterferon alpha-2b, glycosylated interferon alpha-2b, interferon alpha-2c, recombinant interferon alpha-2c, interferon beta, interferon beta-la, peginterferon beta-la, interferon delta, interferon lambda (IFN-λ), peginterferon lambda-1, interferon omega, interferon tau, interferon gamma (IFN-γ), interferon alfacon-1, interferon alpha-nl, interferon alpha-n3, albinterferon alpha-2b, BLX-883, DA-3021, PI 101 (also known as AOP2014), PEG-infergen, Belerofon, INTEFEN-IFN, albumin/interferon alpha 2a fusion protein, rHSA-IFN alpha 2a, rHSA-IFN alpha 2b, PEG-IFN-SA and interferon alpha biobetter; wherein said HBV antiviral of distinct or unknown mechanism is selected from: AT-61 ((E)-N-(1-chloro-3-oxo-1-phenyl-3-(piperidin-1-yl)prop-1-en-2-yl)benzamide), AT130 ((E)-N-(1-bromo-1-(2-methoxyphenyl)-3-oxo-3-(piperidin-1-yl)prop-1-en-2-yl)-4-nitrobenzamide), analogues thereof, REP-9AC (REP-2055), REP-9AC' (REP-2139), REP-2165 and HBV-0259; wherein said cyclophilin inhibitor is preferably selected from: OCB-030 (NVP-018), SCY-635, SCY-575 and CPI-431-32; wherein said HBV polymerase inhibitor is preferably selected from: entecavir (Baraclude, Entavir), lamivudine (3TC, Zeffix, Heptovir, Epivir, and Epivir-HBV), telbivudine (Tyzeka, Sebivo), clevudine, besifovir, adefovir (hepsera), tenofovir, preferably said tenofovir is in a salt form selected from: tenofovir disoproxil fumarate (Viread), tenofovir alafenamide fumarate (TAF), tenofovir disoproxil orotate (DA-2802), tenofovir disopropxil aspartate (CKD-390), AGX-1009, and CMX157; wherein said dinucleotide is preferably SB9200; wherein said SMAC inhibitor is preferably Birinapant; wherein said HDV targeting agent is preferably Lonafamib; wherein said HBV RNA destabilizer or other small-molecule inhibitor of HBV protein expression is preferably RG7834 or AB-452.

14. The pharmaceutical composition according to claim 13 for use in the treatment and/or prevention of a HBV infection.

15. The pharmaceutical composition according to claim 14 for use in treating, eradicating, reducing, slowing or inhibiting an HBV infection in an individual in need thereof, and/or in reducing the viral load associated with an HBV infection in an individual in need thereof, and/or reducing reoccurrence of an HBV infection in an individual in need thereof, and/or inducing remission of hepatic injury from an HBV infection in an individual in need thereof, and/or prophylactically treating an HBV infection in an individual afflicted with a latent HBV infection.

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EUROPEAN SEARCH REPORT

Application Number
EP 18 18 8409

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (IPC)
X,D	WO 2017/001655 A1 (JANSSEN SCIENCES IRELAND UC) 5 January 2017 (2017-01-05) * page 1, line 5 - page 2, line 16; claims; examples * -----	1-15	INV. C07D513/14 C07D515/04 C07D515/14 C07D515/18 C07D519/00 A61K31/554 A61P31/20

TECHNICAL FIELDS SEARCHED (IPC)

C07D
A61K
A61P

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
Munich	25 September 2018	Helps, Ian

CATEGORY OF CITED DOCUMENTS

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This annex lists the patent family members relating to the patent documents cited in the above-mentioned European search report. The members are as contained in the European Patent Office EDP file on
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25-09-2018

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2017001655 A1	05-01-2017	AU 2016287472 A1	30-11-2017
		BR 112017028504 A2	28-08-2018
		CA 2986344 A1	05-01-2017
		CL 2017003459 A1	11-05-2018
		CN 107735400 A	23-02-2018
		CO 2017012268 A2	31-05-2018
		CR 20180069 A	27-06-2018
		EA 201890200 A1	29-06-2018
		EP 3317286 A1	09-05-2018
		JP 2018524333 A	30-08-2018
		KR 20180022818 A	06-03-2018
		PE 4102018 A1	01-03-2018
		PH 12017502316 A1	25-06-2018
		TW 201713635 A	16-04-2017
		US 2017002025 A1	05-01-2017
		UY 36766 A	30-12-2016
		WO 2017001655 A1	05-01-2017

EPO FORM P0459

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REFERENCES CITED IN THE DESCRIPTION

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Patent documents cited in the description

- WO 2013006394 A **[0007]**
- WO 2013096744 A **[0008]**
- WO 2014106019 A **[0009]**
- WO 2014165128 A **[0010]**
- WO 2015109130 A **[0010]**
- US 2015274652 A **[0010]**
- WO 2015120178 A **[0011]**
- WO 2016089990 A **[0012]**
- US 2016185748 A **[0013]**
- US 2016151375 A **[0014]**
- WO 2017001655 A1 **[0014]**
- RO 6864018 **[0049] [0123]**
- RO 7049389 **[0052] [0123]**
- WO 2017001655 A **[0135]**
- US 2006148722 A **[0151]**
- WO 2010016005 A **[0153]**

Non-patent literature cited in the description

- **GUIDOTTI LG ; CHISARI FV.** *Annu Rev Pathol.,* 2006, vol. 1, 23-61 **[0002]**
- **SEEGER C ; MASON WS.** *Virology,* May 2015, vol. 479-480, 672-86 **[0002]**
- **DURANTEL D ; ZOULIM F.** *J Hepatol.,* April 2016, vol. 64 (1), S117-S131 **[0003]**
- **BURNS GS ; THOMPSON AJ.** *Cold Spring Harb Perspect Med.,* 30 October 2014, vol. 4 (12 **[0004]**
- **HUGHES, S.A. et al.** *Lancet,* 2011, vol. 378, 73-85 **[0004]**
- **ZOULIM ; DURANTEL D.** *Cold Spring Harb Perspect Med.,* 01 April 2015, vol. 5 (4 **[0005]**
- **TU M. et al.** *Current Topics in Medicinal Chemistry,* 2013, vol. 13, 857-866 **[0017]**
- Design of Prodrugs. Elsevier, 1985 **[0066]**
- **E.L. ELIEL ; S.H. WILEN.** Stereochemistry of Carbon Compounds. John Wiley & Sons, 1994, 1119-1190 **[0069]**
- **BERG et al.** Pharmaceutical Salts. *J. Pharm. Sci.,* 1977, vol. 66, 1-19 **[0095]**
- **LADNER et al.** *Antimicrob Agents Chemother,* 1997, vol. 41, 1715-20 **[0292]**